

TRANSMITTAL LETTER TO THE UNITED STATES
 DESIGNATED/ELECTED OFFICE (DO/EO/US)
 CONCERNING A FILING UNDER 35 U.S.C. 371

Attorney's Docket Number
 02481.1669

U.S. Application No.
09/554267

PCT.
 4

International Application. No. PCT/EP98/06868	International Filing Date October 29, 1998	Priority Date Claimed November 15, 1997
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Title of Invention: **ANTISENSE OLIGONUCLEOTIDES AGAINST TENASCIN FOR TREATING VITILIGO**

Applicant(s) For DO/EO/US: **Anuschirwan PEYMAN, Eugen UHLMANN, and Caroline WEISER**

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. [] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. [] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. [] is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. [X] has been transmitted by the International Bureau.
 - c. [] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
 - a. [] are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. [] have been transmitted by the International Bureau.
 - c. [] have not been made; however, the time limit for making such amendments has NOT expired.
 - d. [x] have not been made and will not be made.
8. [] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
 [] A SECOND or SUBSEQUENT preliminary amendment.
14. [] A substitute specification.
15. [] A change of power of attorney and/or address letter.
16. [x] Other items or information:
 - a. [] Verified Small Entity Statement.
 - b. [] Copy of Notification of Missing Requirements.
 - c. [x] Sequence Listing (21 sheets)

17. [X] The following fees are submitted:

CALCULATIONS

Basic National Fee (37 CFR 1.492(a)(1)-(5)):

Search Report has been prepared by the EPO or JPO.....\$840.00
 International preliminary examination fee paid to
 USPTO (37 CFR 1.482).....\$670.00
 No international preliminary examination fee paid to
 USPTO (37 CFR 1.482) but international search fee
 paid to USPTO (37 CFR 1.445(a)(2)).....\$690.00
 Neither international preliminary examination fee
 (37 CFR 1.482) nor international search fee
 (37 CFR 1.445(a)(2)) paid to USPTO.....\$970.00
 International preliminary examination fee paid to USPTO
 (37 CFR 1.482) and all claims satisfied provisions
 of PCT Article 33(1)-(4).....\$ 96.00

ENTER APPROPRIATE BASIC FEE AMOUNT = \$840.00

Surcharge of \$130.00 for furnishing the oath or declaration later than
 [] 20 [] 30 months from the earliest claimed priority date
 (37 CFR 1.492(e)).

Claims	Number Filed	Number Extra	Rate	
Total Claims	57-20=	37	X \$18.00	\$666.00
Independent Claims	1 - 3=		X \$78.00	\$
Multiple dependent claim(s) (if applicable)			+\$260.00	\$260.00

TOTAL OF ABOVE CALCULATIONS = \$1766.00

Reduction by 1/2 for filing by small entity, if applicable. Verified
 Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28)

SUBTOTAL = \$1766.00

Processing fee of \$130.00 for furnishing the English translation later
 than [] 20 [] 30 months from the earliest claimed priority date
 (37 CFR 1.492(f)).

TOTAL NATIONAL FEE = \$1766.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The
 assignment must be accompanied by an appropriate cover sheet
 (37 CFR 3.28, 3.31).

\$40.00 per property + \$**TOTAL FEES ENCLOSED = \$1766.00**

Amount to be
 refunded \$
 charged \$

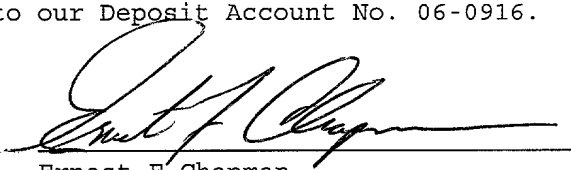
a. [X] A check in the amount of **\$ 1766.00** to cover the above fees is enclosed.b. [] Please charge my Deposit Account No. _____ in the amount of
\$ _____

to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees
which may be required, or credit any overpayment to Deposit Account
No. 06-0916. A duplicate copy of this sheet is enclosed.

The Commissioner is hereby authorized to charge any other fees due under 37 C.F.R. \$1.16
 or \$1.17 during the pendency of this application to our Deposit Account No. 06-0916.

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Submitted: May 12, 2000

PATENT
Attorney Docket No. 02481.1669

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Nat'l Phase Application of)
PCT/EP 98/06868 filed Oct. 29, 1998)
Applicants: Anuschirwan PEYMAN et al.)
Serial No.: Not yet assigned) Group Art Unit: Not yet assigned
Filed: Herewith) Examiner: Not yet assigned
For: ANTISENSE OLIGONUCLEOTIDES)
AGAINST TENASCIN FOR)
TREATING VITILIGO)

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

PRELIMINARY AMENDMENT

Prior to examining this application, please amend this application as follows:

IN THE CLAIMS:

Please cancel Claims 1-23 without prejudice or disclaimer. Please add Claims 24-44, as follows:

24. An oligonucleotide comprising 7 to 17 nucleotides, wherein the oligonucleotide binds to a nucleic acid which codes for one of the isoforms of human tenascin or parts thereof and inhibits its expression, and the physiologically tolerable salts of the oligonucleotide.

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25. The oligonucleotide according to claim 24, wherein the oligonucleotide binds to a region of the nucleic acid which comprises:

- a) a part of the 5'-noncoding region optionally including a translation start,
- b) a translation start optionally including a part of the coding region, or
- c) a part of the coding region optionally including a part of the 3'-noncoding region.

26. The oligonucleotide according to claim 24, comprising a sequence selected from the group consisting of:

- SEQ. ID NO. 2: 3'-GGTTTGGGTGGAGGTGG-5',
- SEQ. ID NO. 3: 3'-GGAGGTGGTACCCCCGG-5',
- SEQ. ID NO. 4: 3'-GGTGGTACCCCCGG-5',
- SEQ. ID NO. 5: 3'-GGAGGTGGTACCCC-5',
- SEQ. ID NO. 6: 3'-AGAAAGAACGAAAGGAA-5',
- SEQ. ID NO. 7: 3'-GGAGGTGGTACC-5',
- SEQ. ID NO. 8: 3'-GGAGCGATGGCTTCCA-5',
- SEQ. ID NO. 9: 3'-AAAGGAACGGGAGCG-5',
- SEQ. ID NO. 10: 3'-GGTCGGTTTGGGTGG-5',
- SEQ. ID NO. 11: 3'-CTTACAGGTCCGTTGA-5',
- SEQ. ID NO. 12: 3'-GGCCGTGTTGCTGT-5',
- SEQ. ID NO. 13: 3'-TCACCCCTCTTCTGG-5',
- SEQ. ID NO. 14: 3'-GGACACCGACACGG-5',
- SEQ. ID NO. 15: 3'-AACGGGAGCGATGG-5',

SEQ. ID NO. 16. 3'- ATCTCGGGGTCGTC -5',
SEQ. ID NO. 17: 3'-AAAGAACGAAAGGAA-5',
SEQ. ID NO. 18: 3'- GGTGGTACCCC -5',
SEQ. ID NO. 19: 3'- CCCGGTACTGA -5', and
SEQ. ID NO. 20: 3'- CCACAGAAAGAAC -5'.

27. An oligonucleotide according to any one of claims 24, 25, or 26, wherein the oligonucleotide has one or more modifications.

28. The oligonucleotide according to claim 27, wherein the modifications are independently selected from the group consisting of:

- a) the replacement of a phosphoric acid diester internucleoside bridge by a modified phospho bridge,
- b) the replacement of a phosphoric acid diester internucleoside bridge by a "dephospho" bridge,
- c) the replacement of a sugar phosphate unit by another unit,
- d) the replacement of a β -D-2'-deoxyribose unit by a modified sugar unit,
- e) the modification or the replacement of a natural nucleoside base by a modified nucleoside base,
- f) the conjugation of the oligonucleotide to a molecule which adapts the properties of the oligonucleotide to a specific requirement,

g) the conjugation of the oligonucleotide to a 2'5'-bonded oligoadenylate or a derivative thereof, optionally conjugated via a linker, and

h) the introduction of a 3'-3' or 5'-5' inversion at the 3' or 5' end of the oligonucleotide.

29. The oligonucleotide according to claim 28, wherein the oligonucleotide contains one or more modification independently selected from the group consisting of:

a) the replacement of a phosphoric acid diester internucleoside bridge by a modified phospho bridge,

where a modified phospho bridge is a phosphorothioate, phosphorodithioate, $\text{NR}^1\text{R}^{1'}$ -phosphoramidate, boranophosphate, phosphate-($\text{C}_1\text{-C}_{21}$)-O-alkyl ester, phosphate-[($\text{C}_6\text{-C}_{12}$)aryl-($\text{C}_1\text{-C}_{21}$)-O-alkyl] ester, ($\text{C}_1\text{-C}_8$)alkylphosphonate, or ($\text{C}_6\text{-C}_{12}$) arylphosphonate bridge,

where

R^1 and $\text{R}^{1'}$ are independently selected from the group comprising hydrogen,

($\text{C}_1\text{-C}_{18}$)-alkyl, ($\text{C}_6\text{-C}_{20}$)-aryl, ($\text{C}_6\text{-C}_{14}$)-aryl-($\text{C}_1\text{-C}_8$)-alkyl, or

R^1 and $\text{R}^{1'}$, together with the nitrogen atom carrying them, form a 5- to

6-membered heterocyclic ring which can additionally contain a further heteroatom

from the group consisting of O, S, and N;

b) the replacement of a phosphoric acid diester internucleoside bridge by a "dephospho" bridge,

where a "dephospho" bridge is a formacetal, 3'-thioformacetal, methylhydroxylamine, oxime, methylenedimethylhydrazo, dimethylenesulfone, or silyl bridge,

c) the complete or partial replacement of the sugar phosphate backbone (replacement of sugar phosphate units) by other units,

where another unit is suitable for synthesizing a "morpholine derivative" oligomer, a polyamide nucleic acid ("PNA"), or a phosphomonoacid ester nucleic acid,

d) the replacement of a β -D-2'-deoxyribose unit by a modified sugar unit,

where a modified sugar unit is an α -D-2'-deoxyribose, L-2'-deoxyribose, 2'-F-2'-deoxyribose, 2'-O-(C₁-C₆)alkylribose, 2'-O-(C₂-C₆)alkenylribose, 2'-[O-(C₁-C₆)alkyl-O-(C₁-C₆)alkyl]ribose, 2'-NH₂-2'-deoxyribose, β -D-xylofuranose, α -arabinofuranose, 2,4-dideoxy- β -D-erythro-hexopyranose, a carbocyclic sugar analog, an open-chain sugar analog, or a bicyclo sugar analog,

e) the replacement of a natural nucleoside base by a modified nucleoside base,

where a modified nucleoside base is 5-(hydroxymethyl)uracil, 5 aminouracil, pseudouracil, dihydrouracil, 5-(C₁-C₆-alkyl)uracil, 5-(C₂-C₆)-alkenyluracil, 5-(C₂-C₆)-alkynyluracil, 5-(C₁-C₆)-alkylcytosine, 5-(C₂-C₆)-alkenylcytosine, 5-(C₂-C₆)-alkynylcytosine, 5-fluorouracil, 5-fluorocytosine, 5-chlorouracil,

5-chlorocytosine, 5-bromouracil, 5-bromocytosine, a 7-deaza-7-substituted purine,
or a 7-deaza-8-substituted purine,

f) conjugation to a molecule,

where the molecule is a polylysine, intercalator, fluorescent molecule, crosslinker,
lipophilic molecule, lipid, steroid, vitamin, polyethylene glycol, oligoethylene
glycol, (C₁₂-C₁₈)-alkyl phosphate diester, or -O-CH₂-CH(OH)-O-(C₁₂-C₁₈)-alkyl
group,

g) conjugation to a 2'5'-linked oligoadenylate or a derivative thereof

where a 2'5'-linked oligoadenylate or a derivative thereof is a 2'5'-linked
triadenylate, 2'5'-linked tetraadenylate, 2'5'-linked pentaadenylate, or cordycepin
(2'5'-linked 3'-deoxyadenylate), where the conjugation optionally takes place via a
linker and where the 5'-end of the 2'5'-linked oligoadenylate optionally contains a
phosphate, diphosphate, or triphosphate group, and

h) the introduction of a 3'-3' or 5'-5' inversion at the 3'- or 5'- end of the oligonucleotide.

30. The oligonucleotide according to claim 28, wherein 1 - 5 terminal internucleoside bridges
are modified at the 5- or 3'- end of the oligonucleotide.

31. The oligonucleotide according to claim 28, wherein the internucleoside bridges located at
the 3'- or 5'- end of nonterminal nucleosides which contain a pyrimidine base are modified.

32. The oligonucleotide according to claim 28, comprising a sequence selected from the group consisting of:

- SEQ ID NO. 21: 3'- GsGsTsTsTGGGTsGGAGGsTsGsG -5',
SEQ ID NO. 22: 3'- GsGsAsGGTsGGTsACsCCsCCsGsG -5',
SEQ ID NO. 23: 3'- GsGsTGGTsACsCsCCsCsGsG -5',
SEQ ID NO. 24: 3'- GsGsAGGTsGGTsACsCsCsC -5,
SEQ ID NO. 25: 3'- AsGsAAAGAAAsCsGAAAGGsAsA -5',
SEQ ID NO. 26: 3'- GsGsAGGTsGGTsAsCsC -5',
SEQ ID NO. 27: 3'- GsGsAGCsGATsGGCsTsTsCsCsA -5',
SEQ ID NO. 28: 3'- AsAsAGGAACsGGGAGsCsG -5',
SEQ ID NO. 29: 3'- GsGsTCGGTsTsTGGGTsGsG -5',
SEQ ID NO. 30: 3'- CsTsTACAGGTsCsCGTsTsGsA -5',
SEQ ID NO. 31: 3'- GsGsCsCGsTGTsTCGCsTsGsT -5',
SEQ ID NO. 32: 3'- TsCsACsCCsCTsCsTTsTsCsTsGsG -5',
SEQ ID NO. 33: 3'- GsGsAsCACsCGACsACsGsG -5',
SEQ ID NO. 34: 3'- AsAsCsGGGAGCGATsGsG -5',
SEQ ID NO. 35: 3'- AsTsCsTCGGGGTsCsGsTsC -5',
SEQ ID NO. 36: 3'- AsAsAGAACsGAAAGGsAsA -5',
SEQ ID NO. 37: 3'- GsGsTGGTsACsCsCsC -5',
SEQ ID NO. 38: 3'- CsCsCsGGTsACsTsGsA -5, and
SEQ ID NO. 39: 3'- CsCsAsCAGAAAGsAsAsC -5',

where "s" indicates the position of a modified internucleoside bridge.

33. The oligonucleotide according to claim 28, comprising a sequence selected from the group consisting of:

- SEQ ID NO. 40: 3'- GyGyTyTyTyGxGxGxTxGxGxAxGyGyTyGyG -5',
SEQ ID NO. 41: 3'- GyGyAyGyGyTxGxGxTxAxCxCxCyCyGyG -5',
SEQ ID NO. 42: 3'- GyGyTxGxGxTxAxCxCxCyCyGyG -5',
SEQ ID NO. 43: 3'- GyGyAyGyGxTxGxGxTxAxCyCyCyC -5',
SEQ ID NO. 44: 3'- AyGyAyAxAxGxAxAxGxGxAxAxAyGyGyAyA -5',
SEQ ID NO. 45: 3'- GyGyAxGxGxTxGxGxTxAyCyC -5',
SEQ ID NO. 46: 3'- GyGyAxGxCxGxGxTxGyGyCyTyTyCyCyA -5',
SEQ ID NO. 47: 3'- AyAyAyGxGxGxAxAxCxGxGyGyAyGyCyG -5',
SEQ ID NO. 48: 3'- GyGyTyCxGxGxTxTxTxGxGyGyTyGyG -5',
SEQ ID NO. 49: 3'- CyTyTyAxCxAxGxGxTxCxGyTyTyGyA -5',
SEQ ID NO. 50: 3'- GyGyCyCxGxTxGxTxTxCxGyCyTyGyT -5',
SEQ ID NO. 51: 3'- TyCyAyCxCxCxTxTxTxTyTyCyTyGyG -5',
SEQ ID NO. 52: 3'- GyGyAyCxAxCxGxGxAxAyCyGyG -5',
SEQ ID NO. 53: 3'- AyAyCyGxGxGxAxAxCxGxAyTyGyG -5',
SEQ ID NO. 54: 3'- AyTyCyTxCxGxGxGxTxCxGyTyC -5',
SEQ ID NO. 55: 3'- AyAyAyGxAxAxCxGxAxAxAyGyGyAyA -5',
SEQ ID NO. 56: 3'- GyGyTxGxGxTxAxCyCyC -5',
SEQ ID NO. 57: 3'- CyCxGxGxTxAxCyTyGyA -5', and
SEQ ID NO. 58: 3'-CyCyAxCxAxGxAxAxAyAyC-5',

where

"x" independently of one another represents a phosphodiester internucleoside bridge or a modified internucleoside bridge and

"y" independently of one another represents the replacement of a sugar phosphate unit or of a β -D-2'-deoxyribose unit, the modified β -D-2'-deoxyribose unit being located at the 3'- end of "y".

PRELIMINARY AMENDMENT
Nat'l Phase Appln. of PCT/EP 98/06868
Attorney Docket No. 02481.1669

34. The oligonucleotide according to claim 33, where "y" represents 2' O-methyl-, 2'-O-propyl- or 2'-methoxyethoxyribose, or a PNA unit.
35. The method for inhibiting the expression of tenascin by administering an oligonucleotide according to any one of claim 24-26.
36. The method for therapeutically treating vitiligo by administering an oligonucleotide according to any one of claims 24-26.
37. The method for therapeutically treating hypopigmentation disorders, psoriasis, cancer, inflammatory disorders, or cardiovascular disorders by administering an oligonucleotide according to any one of claims 24-26.
38. A pharmaceutical comprising an oligonucleotide according to any one of claims 24-26 and, if appropriate, one or more pharmaceutical vehicles, optionally including additives.
39. The method for inhibiting the expression of tenascin by administering an oligonucleotide according to any one of claims 24-26, in combination with photochemotherapy, the transplantation of cultured melanocytes, treatment with steroids, or treatment with placenta extracts.

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40. The method for therapeutically treating vitiligo by administering an oligonucleotide according to any one of claims 24-26, in combination with photochemotherapy, the transplantation of cultured melanocytes, treatment with steroids, or treatment with placenta extracts.
41. A process for the production of a pharmaceutical, wherein an efficacious dose of one or more oligonucleotides according to any one of claims 24-26 is mixed with one or more pharmaceutical vehicles and/or additives.
42. A process for the preparation of an oligonucleotide according to any one of claims 24-26, the oligonucleotide being chemically synthesized on a solid phase.
43. A diagnostic comprising one or more oligonucleotides according to any one of claims 24-26.
44. A test kit comprising one or more oligonucleotides according any one of claims 24-26.

REMARKS

I. Status of the Claims

Original claims 1-23 have been canceled without prejudice or disclaimer. New claims 24-42 have been added to more particularly point out and distinctly claim what Applicants regard as their invention and cure improper multiple dependency of claims. No new matter has been added. The new claims are supported in the original claims and in the application as follows:

Claim No.	Support
24	Claim 1 and Page 3, lines 8-11
25	Claim 2
26	Claim 3
27	Claim 4
28	Claim 5 and Page 8, lines 37-38
29	Claim 6
30	Claim 8
31	Claim 9
32	Claim 10
33	Claim 11
34	Claim 12
35	Claim 13 and Page 3, lines 25-29
36	Page 16, lines 12-13
37	Page 16, lines 13-19
38	Claim 18
39	Claim 19
40	Page 16, lines 28-34
41	Claim 20
42	Claim 21
43	Claim 22
44	Claim 23

PRELIMINARY AMENDMENT
Nat'l Phase Appln. of PCT/EP 98/06868
Attorney Docket No. 02481.1669

II. Conclusion

Applicants await action on the merits. If there are any additional fees due in connection with the filing of this Preliminary Amendment, please charge those fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Carol P. Einaudi
Carol P. Einaudi
Reg. No. 32,220

Dated: May 12, 2000

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Antisense oligonucleotides against tenascin for the treatment of vitiligo

5 The invention relates to specific, optionally modified oligonucleotides
having a length of up to 18 nucleotides, preferably a length of 7-15
nucleotides, which correspond to sections of tenascin-coding sequences
and can bind to these sequences, to their preparation and to the use
thereof, for example for the specific inhibition of the expression of tenascin
and for the production of medicaments which can be used for the treatment
10 of vitiligo.

Vitiligo is understood as meaning an acquired lack of melanocytes, by
means of which hypopigmented areas of skin result, which as a rule are
sharply demarcated and often symmetrically arranged, form one or two
15 spots or cover almost the entire skin. The hair in hypopigmented regions is
normally white and appears white even in the Wood light. The affected skin
sites are susceptible to sunburn. The cause of the disorder is unknown.
Although vitiligo is considered as a disease which is acquired in the course
of life, a familial cluster is occasionally found (autosomally dominant, with
20 incomplete penetrance and variable pronouncement). It can also follow an
unusual physical trauma, in particular a skull injury. The association of
vitiligo with Addison's disease, diabetes mellitus, pernicious anemia or
thyroid gland dysfunction and the increased occurrence of antibodies
against thyroglobulin, cells of the adrenal gland and border cells of the
25 stomach in the serum have led to an immunological or neurochemical
cause being suspected. Antibodies against melanin were found in some
patients.

All available therapeutic methods lead to satisfactory therapeutic results in
30 only some of the patients (F. Wach et al., H+G 71 (1996) 206). The present
therapies (S.P.W. Kumarasinghe, Ceylon Medical Journal 40 (1995) 94)
include photochemotherapies (PUVA) for example with methoxypsoralen,
phenylalanin or khellin, the transplantation of cultured melanocytes,
epidermal grafting, and treatment with steroids or placenta extracts.
35 Recently, treatment with pseudocatalase was reported (Schallreuter et al.,
Dermatology 190 (1995) 223). Small foci can also be covered with
cosmetic make-up or tannic acid solutions.

Poole et al. (British Journal of Dermatol. 137 (1997) 171) were able to show

that the vitiligo-affected skin has a high content of tenascin in comparison with normal skin. The high tenascin content can contribute to the loss of pigmentation and prevent repigmentation. Tenascin (Crossin, J. Cell. Biol. 61 (1996) 592) is an extracellular matrix glycoprotein, which consists of six
 5 identical subunits which are linked to the amino terminus via disulfide bridges. The tenascin subunits have a characteristic domain structure: a cysteine-rich sequence at the amino-terminal end is followed by three sequence sections, in each case constructed of repeating units, made of units homologous to EGF, of units homologous to fibronectin (type III) and
 10 of units homologous to fibrinogen.

A number of isoforms of the tenascin subunits exists (designated below as tenascin isoforms), which differ in the number of repeating units which are homologous to fibronectin type III. These isoforms are formed by
 15 alternative splicing of the tenascin pre-mRNA and subsequent translation of the various splice variants (A. Leprini et al., Perspectives in Developmental Neurobiology 2 (1994) 117-123). A cDNA from human tenascin was described (sequence in Table 1) by A. Siri et al. (Nucl. Acids Res. 19 (1991) 525-531). This cDNA is stored under the accession number X56160
 20 in gene databases and can be obtained under this number, for example under EMBL/Genbank/DDBJ/NBRF-PIR. This cDNA contains a sequence section which codes for 12 repeating units which are homologous to fibrinogen type III. The cDNAs of the other isoforms of human tenascin are truncated in this sequence section and code for less than 12 of these
 25 repeating units.

The expression of tenascin is limited spatially and temporally and a significance is ascribed to it during the development of an organism and in pathological changes (Crossin, vide supra). Such pathological changes are,
 30 for example, vitiligo, tumors and inflammation.

Antisense oligonucleotides offer one possibility for the regulation of gene expression (E. Uhlmann and A. Peyman, Chemical Reviews 90, 543 (1990); S. Agrawal. TIBTECH 1996, 376). WO 94/21664 (L. Denner et al.)
 35 describes antisense oligonucleotides against tenascin, which are employed for the inhibition of the proliferation of the smooth cell musculature. The oligonucleotides described there have a length of at least 18 nucleotides.

It was an object of the present invention to make available novel oligonucleotides which have advantageous properties and which can be used for the complete and/or partial inhibition of the gene expression of tenascin.

5

It has surprisingly been found that oligonucleotides which have a length of up to 18 nucleotides can effectively influence the expression of tenascin. The present invention relates to oligonucleotides having 7-17 nucleotide units which are optionally modified. In particular embodiments of the invention, the oligonucleotide has a length of 17, 16, 15, 14, 13, 12, 11, 10, 9, 8 or 7 nucleotides. The oligonucleotide corresponds to sections of tenascin-coding sequences (i.e. the oligonucleotide has a sequence which is complementary to the corresponding section of a tenascin-coding sequence) and the oligonucleotide binds specifically to this tenascin-coding sequence (nucleic acid), for example to the tenascin gene and/or tenascin mRNA and/or tenascin cDNA, the tenascin-coding sequence preferably being of human origin (e.g. human tenascin gene, human tenascin mRNA, human tenascin cDNA). The section of the tenascin-coding sequence which corresponds to the oligonucleotide or is complementary to the oligonucleotide preferably has a length of 17, 16, 15, 14, 13, 12, 11, 10, 9, 8 or 7 nucleotide units (this applies in particular to the determination of the length of a modified and/or chimeric oligonucleotide or of oligonucleotide analogs).

25 A particular embodiment of the invention relates to an oligonucleotide which binds to a nucleic acid which codes for one of the isoforms of human tenascin or parts thereof and inhibits its expression, where the oligonucleotide has a length of 7 to 15 nucleotides and can optionally be modified, and the physiologically tolerable salts of the oligonucleotide.

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A particular embodiment of the invention relates to an oligonucleotide which is directed against one or more specific regions of a tenascin-coding sequence, for example the translation start, the 5'-nontranslated region, the coding region and/or the 3'-noncoding region. In a particular embodiment of the invention, the oligonucleotide can also be directed against one or more regions of a tenascin-coding sequence which codes, for example, for certain domains of the tenascin, for example against the cysteine-rich domain, against a domain homologous to EGF, against a domain

35

homologous to fibronectin type III and/or against a domain homologous to fibrinogen.

- 5 One embodiment of the invention relates to an oligonucleotide which binds to a nucleic acid which codes for one of the isoforms of human tenascin or parts thereof and inhibits its expression, where the oligonucleotide can bind to a region of the nucleic acid which comprises
- 10 a) a part of the 5'-noncoding region and/or the translation start or
 - b) the translation start and/or a part of the coding region or
 - c) a part of the coding region and/or a part of the 3'-noncoding region.
- 15 The invention relates in particular to an oligonucleotide which corresponds to a sequence section of the human cDNA according to SEQ ID NO. 1 (Table 1). The invention furthermore relates to an oligonucleotide which corresponds to a sequence section of the cDNA which is stored in gene databases under the accession number X56160.
- 20 In specific embodiments of the invention, an oligonucleotide can have, for example, one of the following sequences or parts thereof:

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SEQ ID NO. 2: 3'-GGTTTGGGTGGAGGTGG -5'
 SEQ ID NO. 3: 3'-GGAGGTGGTACCCCCGG -5'
 SEQ ID NO. 4: 3'-GGTGGTACCCCCGG -5'
 SEQ ID NO. 5: 3'-GGAGGTGGTACCCC -5'
 SEQ ID NO. 6: 3'-AGAAAGAACGAAAGGAA -5'
 SEQ ID NO. 7: 3'-GGAGGTGGTACC -5'
 SEQ ID NO. 8: 3'-GGAGCGATGGCTTCCA -5'
 SEQ ID NO. 9: 3'-AAAGGAACGGGAGCG -5'
 SEQ ID NO. 10: 3'-GGTCGGTTTGGGTGG -5'
 SEQ ID NO. 11: 3'-CTTACAGGTCCGTTGA -5'
 SEQ ID NO. 12: 3'-GGCCGTGTTCTGCTGT -5'
 SEQ ID NO. 13: 3'-TCACCCCTCTTTCTGG -5'
 SEQ ID NO. 14: 3'-GGACACCGACACGG -5'
 SEQ ID NO. 15: 3'-AACGGGAGCGATGG -5'
 SEQ ID NO. 16: 3'-ATCTCGGGGTCGTC -5'
 SEQ ID NO. 17: 3'-AAAGAACGAAAGGAA -5'
 SEQ ID NO. 18: 3'-GGTGGTACCCC -5'
 SEQ ID NO. 19: 3'-CCCGGTACTGA -5' and
 SEQ ID NO. 20: 3'-CCACAGAAAGAAC -5'.

5 The sequences SEQ ID NO. 2 to SEQ ID NO. 20 correspond to sections of the tenascin-coding cDNA, as is shown in Table 1. An oligonucleotide which has one of the sequences SEQ ID NO. 2 to SEQ ID NO. 20 is complementary to a corresponding section of a tenascin-coding nucleic acid, e.g. a human tenascin cDNA, and can bind to this nucleic acid. Sequences SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 7 and SEQ ID NO. 18 are examples of oligonucleotides which have a sequence which is directed against the translation start of the tenascin-coding sequences.

15 The invention also relates to derivatives of an oligonucleotide, for example its salts, in particular its physiologically tolerable salts. Physiologically tolerable salts are understood as meaning compounds which are readily soluble, soluble or poorly soluble in water, for example according to the definition in the "Deutsches Arzneibuch" [German Pharmacopeia] (9th

Edition 1986, official edition, Deutscher Apotheker Verlag Stuttgart), page 19. A specific embodiment of the invention relates to the sodium salt of the oligonucleotide according to the invention. Derivatives are also modified oligonucleotides.

5

An oligonucleotide can be synthesized completely or partially from the natural nucleotides adenosine phosphate, guanosine phosphate, inosine phosphate, cytidine phosphate, uridine phosphate and thymidine phosphate. One embodiment of the invention relates to an oligonucleotide

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which is synthesized from the natural nucleotides adenosine, guanosine, inosine, cytidine, uridine and thymidine and in which the nucleosides are linked to one another via phosphoric acid diester internucleoside bridges ("phosphoric acid diester bridges").

15

In other embodiments of the invention, an oligonucleotide can optionally contain one or more modifications, for example chemical modifications. An oligonucleotide can have a number of identical and/or different modifications. Modifications can be localized on certain nucleotide positions (nucleobase and/or β -D-2'-deoxyribose unit) and/or certain internucleoside

20

bridges.

Examples of chemical modifications are known to the person skilled in the art and are described, for example, in E. Uhlmann and A. Peyman, Chemical Reviews 90 (1990) 543 and "Protocols for Oligonucleotides and

25

Analogs" Synthesis and Properties & Synthesis and Analytical Techniques, S. Agrawal, Ed, Humana Press, Totowa, USA 1993, S.T. Crooke, F. Bennet, Ann. Rev. Pharmacol. Toxicol. 36 (1996) 107-129 and J. Hunziber and C. Leumann (1995) Mod. Synt. Methods, 7, 331-417.

30

The chemical modification of an oligonucleotide can mean, for example, a) the complete or partial replacement of the phosphoric acid diester bridges (internucleoside bridges) by modified phospho bridges, phosphorothioate, phosphorodithioate, $\text{NR}^1\text{R}^{1'}$ -phosphoramidate, boranophosphate, phosphate-(C₁-C₂₁)-O-alkyl ester, phosphate-[(C₆-C₁₂)-aryl-(C₁-C₂₁)-O-alkyl] ester, (C₁-C₈)alkylphosphonate and/or (C₆-C₁₂)-arylphosphonate bridges being examples of modified phospho bridges, where

35

R^1 and $\text{R}^{1'}$ independently of one another are hydrogen, (C₁-C₁₈)-alkyl, (C₆-C₂₀)-aryl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl, preferably hydrogen, (C₁-C₈)-

alkyl and/or methoxyethyl, particularly preferably hydrogen, (C₁-C₄)-alkyl and/or methoxyethyl

or

R¹ and R^{1'}, together with the nitrogen atom carrying them, form a 5- to 6-

- 5 membered heterocyclic ring, which can additionally contain a further heteroatom from the group consisting of O, S and N;

and/or

- b) the complete or partial replacement of the 3' and/or 5' phosphoric acid diester internucleoside bridges ("phosphoric acid diester bridges") by
 10 "dephospho" bridges (described, for example, in Uhlmann, E. and Peyman, A. in "Methods in Molecular Biology", Vol. 20, "Protocols for Oligonukleotides and Analogs", S. Agrawal, Ed., Humana Press, Totowa 1993, Chapter 16, 355ff), formacetal, 3'-thioformacetal, methylhydroxylamine, oxime, methylenedimethylhydrazo, dimethylenesulfone and/or silyl
 15 groups being examples of dephospho bridges;

and/or

- c) the complete or partial replacement of the sugar phosphate backbone (replacement of sugar phosphate units) by other units, the other unit being
 20 suitable, for example, to synthesize a "morpholine derivative" oligomer (described, for example, in E.P. Stirchak et al., Nucleic Acids Res. 17 (1989) 6129) (i.e. replacement by a morpholino derivative unit) and/or being suitable to synthesize a polyamide nucleic acid ("PNA") described, for example, in P.E. Nielsen et al., Bioconj. Chem. 5 (1994) 3 (EP 0 672 677) (i.e. replacement by a PNA unit, for example 2-aminoethylglycine) and/or being suitable to synthesize a phosphomonoacid ester
 25 nucleic acid ("PHONA", "PMENA") (described, for example, in Peyman et al., Angew. Chem. Int. Ed. Engl. 35 (1996) 2632-2638, EP 0 739 898) (i.e. replacement by a PHONA unit);

and/or

- d) the complete or partial replacement of the β -D-2'-deoxyribose (β -D-2'-deoxyribose unit) by modified sugar units, α -D-2'-deoxyribose, L-2'-deoxyribose, 2'-F-2'-deoxyribose, 2'-O-(C₁-C₆)alkylribose, preferably 2'-O-methylribose, 2'-O-(C₂-C₆alkenylribose, 2'-[O-(C₁-C₆) alkyl-O-(C₁-C₆alkyl)-ribose, 2'-NH₂-2'-deoxyribose, β -D-xylofuranose, α -arabinofuranose, 2,4-dideoxy- β -D-erythrohexopyranose, carbocyclic sugar analogs (described,
 35 for example, in Froehler, J.Am.Chem.Soc. 114 (1992) 8320), open-chain sugar analogs (described, for example, in Vandendriessche et al., Tetrahedron 49 (1993) 7223) and bicyclo sugar analogs (described, for

analogues (described, for example, in M. Tarkov et al., *Helv. Chim. Acta* 76 (1993) 481) being examples of modified sugar units;
and/or

- e) the modification or the complete or partial replacement of the natural nucleoside bases by modified (nucleoside) bases ("nucleobases"), 5- (hydroxymethyl)uracil, 5-aminouracil, pseudouracil, dihydrouracil, 5-(C₁-C₆-alkyl)uracil, 5-(C₂-C₆)-alkenyluracil, 5-(C₂-C₆)alkynyluracil, 5-(C₁-C₆)alkylcytosine, 5-(C₂-C₆)alkenylcytosine, 5-(C₂-C₆)alkynylcytosine, 5-fluorouracil, 5-fluorocytosine, 5-chlorouracil, 5-chlorocytosine, 5-bromouracil, 5-bromocytosine, 7-deaza-7-substituted purines, 7-deaza-8-substituted purines, 8-azapurines, 2,4-diaminopurines, 5-bromocytosine, 5-bromouracil, 5-chlorocytosine, 5-chlorouracil, 5-fluorocytosine, 5-fluorouracil, hypoxanthine and uracil being examples of modified bases;
and/or
- f) the conjugation to one or more molecules (oligonucleotide conjugates) which adapt the property(ies) of the oligonucleotide to specific requirements or favorably influence the properties (e.g. cell penetration, nuclease stability, affinity for the tenascin-coding target sequence, pharmacokinetics) of the oligonucleotide (e.g. antisense oligonucleotide, triple helix-forming oligonucleotide) and/or in the hybridization of the oligonucleotide on the target sequence can attack this with binding and/or crosslinking, polylysine, intercalators such as pyrene, acridine, phenazine, phenanthridine, fluorescent compounds such as fluorescein, crosslinkers such as psoralen, azidoproflavine, lipophilic molecules such as (C₁₂-C₂₀)alkyl, lipids such as 1,2-dihexadecyl-rac-glycerol, steroids such as cholesterol, testosterone, vitamins such as vitamin E, poly- or oligoethylene glycol, (C₁₂-C₁₈)alkyl phosphate diesters and -O-CH₂-CH(OH)-O-(C₁₂-C₁₈)-alkyl being examples of molecules which can be conjugated to an oligonucleotide, where such molecules can be conjugated to the oligonucleotide at the 5' and/or at the 3' end and/or within the sequence, e.g. via a nucleobase;
and/or
- g) the conjugation to a 2'5'-linked oligoadenylate or a derivative thereof, a 2'5'-linked triadenylate, a 2'5'-linked tetraadenylate, a 2'5'-linked pentaadenylate etc. being examples of 2'5'-linked oligoadenylates and cordycepin (2'5'-linked 3'-deoxyadenylate) being an example of a derivative of a 2'5'-linked oligoadenylate, the conjugation preferably taking place via a linker, where the 5'-end of the 2'5'-linked oligoadenylate can preferably be a phosphate, diphosphate or triphosphate group, where the linker, for

example, can be an oligoethylene glycol, triethylene glycol, tetraethylene glycol and hexaethylene glycol being examples of oligoethylene glycol linkers;
and/or

- 5 h) the introduction of a 3'-3' and/or 5'-5' inversion at the 3' and/or at the 5' end of the oligonucleotide, this type of chemical modification being known to the person skilled in the art and being described, for example, in M. Koga et al., J. Org. Chem. 56 (1991) 3757.
- 10 In preferred embodiments of the invention, the oligonucleotide has one or more chemical modifications which independently of one another are selected from
 - a) the complete or partial replacement of the phosphoric acid diester bridges by phosphorothioate and/or (C₁-C₈)alkylphosphonate bridges,
 - 15 b) the complete or partial replacement of the sugar phosphate backbone by PNA units and/or PHONA units,
 - c) the complete or partial replacement of the β -D-2'-deoxyribose units by 2'-F-2'-deoxyribose, 2'-O-(C₁-C₆)alkylribose and/or 2'-[O-(C₁-C₆)alkyl-O-(C₁-C₆)alkyl]ribose,
 - 20 d) the complete or partial replacement of the natural nucleoside bases by 5-(C₂-C₆)-alkynyluracil and/or 5-(C₂-C₆)alkynylcytosine,
 - e) the conjugation of the oligonucleotide to one or more molecules which independently of one another can be selected from the group comprising lipophilic molecules, e.g. (C₁₂-C₂₀)alkyl, lipids, e.g. 1,2-
25 dihexadecyl-rac-glycerol, steroids, e.g. cholesterol and/or testosterone, vitamins, e.g. vitamin E, poly- or oligoethylene glycol, (C₁₂-C₁₈)-alkyl phosphate diesters and -O-CH₂-CH(OH)-O-(C₁₂-C₁₈)-alkyl and
f) one or more 3'-3' inversions at the 3' end of the oligonucleotide,In another preferred embodiment of the invention, the oligonucleotide has
30 one or more chemical modifications which independently of one another can be selected from the group comprising
 - a) the complete or partial replacement of the phosphoric acid diester bridges (phosphodiester bridges) by phosphorothioate bridges,
 - b) the complete or partial replacement of the β -D-2'-deoxyribose units
35 by 2'-F-2'-deoxyribose, 2'-O-(C₁-C₆)alkylribose and/or 2'-[O-(C₁-C₆)alkyl-O-(C₁-C₆)alkyl]ribose,
 - c) conjugation to lipophilic molecules, e.g. (C₁₂-C₂₀)-alkyl, to lipids, e.g. 1,2-dihexadecyl-rac-glycerol, to (C₁₂-C₁₈)alkyl phosphate diesters and/ or to -O-CH₂-CH(OH)-O-(C₁₂-C₁₈)-alkyl.

Processes for the preparation of an oligonucleotide conjugate are known to the person skilled in the art and are described, for example, in Uhlmann, E. & Peyman, A., Chem. Rev. 90 (1990) 543 and/or M. Manoharan in
 5 "Antisense Research and Applications", Crooke and Lebleu, Eds., CRC Press, Boca Raton, 1993, Chapter 17, p.303ff. and/or EP-A 0 552 766.

In a particular embodiment of the invention, an oligonucleotide is made available which can have one or more modifications and which has one of
 10 the sequences SEQ ID NO. 2 - SEQ ID NO. 20 or which corresponds to one of the sequences SEQ ID NO. 2 to SEQ ID NO. 20 or which corresponds to the appropriate sequence sections of a tenascin-coding sequence and can bind to this section of the tenascin-coding sequence.

15 In a particular embodiment of the invention, oligonucleotide is made available in whose sequence each nucleotide (base and/or sugar and/or internucleoside bridge) is modified. In a particular embodiment of the invention, for example, the oligonucleotide is completely synthesized from phosphorothioates (universally modified phosphorothioate, all
 20 internucleoside bridges modified). In a further specific embodiment of the invention, an oligonucleotide is made available which corresponds to one of the sequences SEQ ID NO. 2 - SEQ ID NO. 20, but where the phosphodiester bridges between the individual nucleosides (i.e. the internucleoside bridges between the individual nucleosides) are completely
 25 replaced by phosphorothioate bridges (i.e. phosphorothioate groups between the nucleosides).

In a further particular embodiment of the invention, an oligonucleotide is made available by only replacing some of the phosphodiester bridges by
 30 phosphorothioate bridges. In particular, the invention comprises oligonucleotides which are only minimally (or partially) modified. The principle of the minimally modified oligonucleotides is described in A. Peyman, E. Uhlmann, Biol. Chem. Hoppe-Seyler, 377 (1996) 67-70. In this case, 1-5, preferably 1-3 terminal nucleotide units (preferably the
 35 corresponding internucleoside bridges) at the 5' and/or at the 3' end and, if appropriate, additionally selected internal pyrimidine positions or preferably the corresponding internucleoside bridges which are located at the 3' and/or 5' end of the corresponding pyrimidine nucleoside, are modified or replaced, internucleoside bridges preferably being replaced by

phosphorothioate bridges. Oligonucleotides minimally modified in this way have particularly advantageous properties, for example they exhibit particular nuclease stability on minimal modification.

- 5 A particular embodiment of the invention relates to an oligonucleotide in which selected internucleoside bridges are replaced by modified internucleoside bridges, preferably by phosphorothioate bridges.

The invention relates to an oligonucleotide in which either

- 10 a) only certain phosphodiester internucleoside bridges or
b) all phosphodiester internucleoside bridges
are modified.

The invention furthermore relates to an oligonucleotide in which 1 – 5 terminal internucleoside bridges are modified at the 5' and/or at the 3' end

- 15 of the oligonucleotide. The invention also relates to an oligonucleotide in which the internucleoside bridges located at the 3' and/or 5' end of nonterminal nucleosides which contain a pyrimidine base (internal pyrimidine nucleosides) are modified.

- 20 Specific embodiments of the invention comprise a minimally modified oligonucleotide which has one of the sequences selected from the group consisting of the sequences SEQ ID NO. 21 to SEQ ID NO. 39, where

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SEQ ID NO. 21: is 3'- GsGsTsTsTGGGTsGGAGGsTsGsG -5',
 SEQ ID NO. 22: is 3'- GsGsAsGGTsGGTACsCCsCCsGsG -5',
 SEQ ID NO. 23: is 3'- GsGsTGGTACsCsCCsCsGsG -5',
 SEQ ID NO. 24: is 3'- GsGsAGGTsGGTACsCsCsC -5',
 SEQ ID NO. 25: is 3'- AsGsAAAGAAcCsGAAAGGsAsA -5',
 SEQ ID NO. 26: is 3'- GsGsAGGTsGGTAsCsC -5',
 SEQ ID NO. 27: is 3'- GsGsAGCsGATsGGCsTsTsCsCsA -5',
 SEQ ID NO. 28: is 3'- AsAsAGGAACsGGGAGsCsG -5',
 SEQ ID NO. 29: is 3'- GsGsTCGGTsTsTGGGTsGsG -5',
 SEQ ID NO. 30: is 3'- CsTsTACAGGTsCsCGTsTsGsA -5',
 SEQ ID NO. 31: is 3'- GsGsCsCGsTGTsTCGCsTsGsT -5',
 SEQ ID NO. 32: is 3'- TsCsACsCCsCTsCsTTsTsCsTsGsG -5',
 SEQ ID NO. 33: is 3'- GsGsAsCACsCGACsACsGsG -5',
 SEQ ID NO. 34: is 3'- AsAsCsGGGAGCGATsGsG -5',
 SEQ ID NO. 35: is 3'- AsTsCsTCGGGGTsCsGsTsC -5',
 SEQ ID NO. 36: is 3'- AsAsAGAACsGAAAGGsAsA -5',
 SEQ ID NO. 37: is 3'- GsGsTGGTACsCsCsC -5',
 SEQ ID NO. 38: is 3'- CsCsCsGGTACsTsGsA -5',
 SEQ ID NO. 39: is 3'- CsCsAsCAGAAAGsAsAsC-5' and

5 "s" indicating the position of a modified internucleoside bridge or dephospho bridge; "s" preferably indicating the position of a phosphorothioate bridge.

10 The sequences SEQ ID NO. 21 to SEQ ID NO. 39 correspond to the sequences SEQ ID NO. 2 - SEQ ID NO. 20, i.e. they can bind to the same regions of a tenascin-coding sequence, where, however, in contrast to the SEQ ID NO. 2-20, some of the phosphodiester bridges are replaced by modified phosphodiester bridges or dephospho bridges, preferably by phosphorothioate bridges (in the sequence marked by an "s").

15 A further embodiment of the invention relates to chimeric oligonucleotides. A chimeric oligonucleotide is synthesized from at least two different sequence sections, for example from a DNA section and a modified section, e.g. a PNA section and/or a PHONA section. These different sections impart particular properties to the entire oligonucleotide.

A particular form of chimeric oligonucleotides is described, for example, in Matteucci and Wagner, Nature 384 SUPP (1996) 20-22. A chimeric oligonucleotide can contain, for example,

1. a so-called core sequence, which consists of approximately seven nucleotides and which can activate the RNase H, and
2. one or more flanking sequences which increase the affinity, specificity and/or nuclease stability of the oligonucleotide.

For example, the core sequence can have internucleoside bridges modified in certain positions, for example the core sequence can contain phosphorothioate and/or phosphodiester bridges. Suitable flanking sequences are, for example, sequences in which the sugar phosphate backbone (replacement of one or more sugar phosphate units) and/or β -D-2'-deoxyribose units are replaced. Suitable flanking sequences are, for example, PNAs and/or 2'-O-alkyl derivatives such as, for example, 2'-O-methyl and/or 2'-O-propyl and/or 2'-methoxyethoxy derivatives.

A particular embodiment of the invention relates to a chimeric oligonucleotide which has one of the sequences SEQ ID NO. 40 - SEQ ID NO. 58, where

- x independently of one another represents an unmodified or a modified phosphodiester internucleoside bridge or a dephospho bridge, preferably phosphorothioate and/or phosphorus diester
 - and
 - y independently of one another represents the replacement of a sugar phosphate unit or a β -D-2'-deoxyribose unit, preferably 2'-O-methyl-, 2'-O-propyl- and/or 2'-methoxyethoxyribose or a PNA unit,
- where

SEQ ID NO. 40: is 3'- GyGyTyTyTyGxGxGxTxGxGxAxGyGyTyGyG -5',
 SEQ ID NO. 41: is 3'- GyGyAyGyGyTxGxGxTxAxCxCxCyCyGyG -5',
 SEQ ID NO. 42: is 3'- GyGyTxGxGxTxAxCxCxCxCyCyGyG -5',
 SEQ ID NO. 43: is 3'- GyGyAyGyGxTxGxGxTxAxCyCyCyC -5',
 SEQ ID NO. 44: is 3'- AyGyAyAxAxGxAxAxCxGxAxAxGyGyAyA -5',
 SEQ ID NO. 45: is 3'- GyGyAxGxGxTxGxGxTxAyCyC -5',
 SEQ ID NO. 46: is 3'- GyGyAxGxCxGxAxTxGyGyCyTyTyCyCyA -5',
 SEQ ID NO. 47: is 3'- AyAyAyGxGxAxAxCxGxGyGyAyGyCyG -5',
 SEQ ID NO. 48: is 3'- GyGyTyCxGxGxTxTxTxGxGyGyTyGyG -5',
 SEQ ID NO. 49: is 3'- CyTyTyAxCxAxGxGxTxCxCxGyTyTyGyA -5',
 SEQ ID NO. 50: is 3'- GyGyCyCxGxTxGxTxTxCxGyCyTyGyT -5',
 SEQ ID NO. 51: is 3'- TyCyAyCxCxCxTxTxTxTyTyCyTyGyG -5',
 SEQ ID NO. 52: is 3'- GyGyAyCxAxCxCxGxAxCxGyGyG -5',
 SEQ ID NO. 53: is 3'- AyAyCyGxGxGxAxGxCxGxAyTyGyG -5',
 SEQ ID NO. 54: is 3'- AyTyCyTxCxGxGxGxTxTxGyTyC -5',
 SEQ ID NO. 55: is 3'- AyAyAyGxAxAxCxGxAxAxGyGyAyA -5',
 SEQ ID NO. 56: is 3'- GyGyTxGxGxTxAxCxCyCyC -5',
 SEQ ID NO. 57: is 3'- CyCxCxGxGxTxAxCyTyGyA -5',
 SEQ ID NO. 58: is 3'- CyCyAxCxAxGxAxAxGyAyAyC -5'

5 The sequences SEQ ID NO. 40 - SEQ ID NO. 58 correspond to the abovementioned sequences SEQ ID NO. 2 to SEQ ID NO. 20, i.e. they bind to the corresponding sequence sections of a tenascin-coding sequence, where, however, the modifications mentioned are present.

10 The invention relates to processes for the preparation of the oligonucleotides. The oligonucleotides described can be prepared with the aid of various known, chemical processes, e.g. applying the standard phosphoramidite chemistry using iodine or TED (tetraethylthiuram disulfide) as oxidant. This process is described, for example, in Eckstein, F. (1991) "Oligonucleotides and Analogues, A Practical Approach", IRL Press, Oxford. The oligonucleotides can also be prepared by processes which
 15 optionally contain one or more enzymatic steps.

The invention relates to the use of the oligonucleotides. The oligonucleotides can be used for hybridization or binding to tenascin-coding (single-stranded and/or double-stranded) nucleic acids, for example DNA

relates to the use of the oligonucleotides for hybridization with or binding to nucleic acids which have the sequence SEQ ID NO. 1 according to Table 1 or with nucleic acids which have parts of this sequence (for example sequences which code for tenascin isoforms) or with nucleic acids whose
5 sequence differs slightly from these sequences (which have, for example, one or more point mutations).

The invention furthermore relates to the use of the oligonucleotides for the modulation and for the complete or partial inhibition of the expression of
10 tenascin or various tenascin isoforms or of mutants thereof, for example for the complete or partial inhibition of transcription and/or of translation.

The invention relates, for example, to the use of the oligonucleotides as antisense oligonucleotides. Moreover, the oligonucleotides can be used as
15 aids in molecular biology.

The invention furthermore relates to the use of the oligonucleotides as pharmaceutical and/or diagnostic or the use of the oligonucleotides for the production of pharmaceuticals and/or diagnostics. In particular, the
20 oligonucleotides can be employed in pharmaceuticals which are suitable for the prevention and/or treatment of diseases which accompany the expression of an overexpression of tenascin. Since the expression of tenascin is normally, i.e., for example, in the healthy person, limited spatially and temporally, a deviation from this normal spatial and temporal
25 expression can be regarded as overexpression. Furthermore, the oligonucleotides can be employed in diagnostic processes. Such diagnostic processes can be employed, for example, for the diagnosis or early recognition of diseases which accompany abnormal expression (e.g. overexpression) of tenascin.

30 The invention also relates to a test kit which contains one or more oligonucleotides according to the invention and, if appropriate, further components. Such a test kit can be employed, for example, in diagnosis and as a precaution, for example against skin cancer disorders.

35 The invention further relates to the use of the oligonucleotides or of pharmaceuticals which contain these oligonucleotides for the treatment of diseases in which tenascin or an overexpression of tenascin is the cause or is involved.

The invention relates in particular to the use of the oligonucleotides or of pharmaceuticals which contain these oligonucleotides for the treatment and/or prevention of diseases in which a dysregulation or disorder of the immigration or of the presence or of the inclusion of melanocytes in epithelial cell layers, for example in the epithelial cell layer of the epidermis, of the choroid membrane of the eye or of the substantia nigra as the basis serves or is involved and of Addison's disease, diabetes mellitus, pernicious anemia and/or thyroid gland dysfunctions.

10

The invention relates in particular to the use of the oligonucleotides or of pharmaceuticals which contain these oligonucleotides for the treatment and/or prevention of vitiligo and other depigmentation diseases or depigmentation disorders (e.g. of the skin, hair, eyes) for example albinism and/or for the treatment of psoriasis and/or for the treatment of cancer, e.g. for the inhibition of tumor growth and tumor metastasis, for example in melanomas and/or for the treatment of inflammations, in particular as antiinflammatories and/or for the treatment and/or prophylaxis of cardiovascular disorders, for example of restenosis.

20

In particular, the invention relates to the use of the oligonucleotides for the treatment of vitiligo or for the production of pharmaceuticals which can be used for the treatment of vitiligo. The invention moreover relates quite generally (i.e. also oligonucleotides having a length of greater than or equal to 18 nucleotides) to the use of oligonucleotides for the treatment of vitiligo or the production of pharmaceuticals which can be used for the treatment of vitiligo.

25

The invention furthermore relates to the use for the treatment of vitiligo in combination with known therapeutic processes, for example in combination a) with photochemotherapy (PUVA), e.g. using methoxypsoralen, phenylalanine and/or khellin and/or b) with the transplantation of cultured melanocytes (epidermal grafting) and/or c) with a steroid treatment and/or d) with a treatment with placenta extracts and/or e) with a treatment with pseudocatalase.

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The invention furthermore relates to processes for the production of pharmaceuticals (pharmaceutical preparations). For the production of pharmaceuticals, one or more different oligonucleotides or their

physiologically tolerable salts are mixed, it optionally being possible to add further pharmaceutical vehicles and/or additives.

5 The invention furthermore relates to pharmaceutical preparations (pharmaceuticals), which contain one or more different oligonucleotides and/or their physiologically tolerable salts, and, if appropriate, pharmaceutical vehicles and/or additives.

10 The oligonucleotide(s) and/or its/their physiologically tolerable salts can be administered to animals, preferably to mammals, in particular to humans as pharmaceuticals on its/their own, in mixtures with one another or in the form of pharmaceutical preparations. The pharmaceuticals can make possible topical, percutaneous, parenteral and/or enteral administration. The administration form preferred in each case depends on the specific
15 conditions in each case. For the treatment of vitiligo, for example, a topical application, e.g. in the form of ointments, lotions or tinctures, emulsions or suspensions, is preferred. Likewise, the frequency of the administration depends on the individual conditions. For the treatment of vitiligo, for example, a topical composition can be applied to the depigmented skin site
20 one to two times during the day.

As active constituent, pharmaceuticals or pharmaceutical preparations can contain an efficacious dose of at least one oligonucleotide and/or a mixture of a number of oligonucleotides and, if appropriate, additional,
25 pharmaceutically innocuous vehicles and/or additives. Pharmaceutical preparations can contain approximately 0.1% (percent by weight) or less up to approximately 90% (percent by weight) or more of the therapeutically active oligonucleotide or the pharmaceutically active oligonucleotide.

30 The pharmaceutically efficacious dose of the respective oligonucleotide or of an oligonucleotide which is a constituent of a mixture of various oligonucleotides can vary within wide limits and is to be adapted to the individual conditions in each individual case.

35 The production of the pharmaceutical preparations can be carried out in a manner known per se, e.g. described in Remingtons Pharmaceutical Sciences (1985), Mack Publ. Co., Easton, PA., it optionally being possible to use pharmaceutically inert inorganic and/or organic vehicles. For the production of pills, tablets, coated tablets and/or hard gelatin capsules, it is

possible to use, for example, lactose, cornstarch and/or derivatives thereof, talc, stearic acid and/or its salts. Vehicles which can be used for soft gelatin capsules and/or suppositories are, for example, fats, waxes, semisolid and/or liquid polyols, natural and/or hardened oils. Vehicles which can be used for the production of solutions and/or syrups are, for example, water, sucrose, invert sugar, glucose and/or polyols. Vehicles which can be used for the production of injection solutions are, for example, water, alcohols, glycerol, polyols and/or vegetable oils. Vehicles which can be used for microcapsules, implants and/or rods are, for example, copolymers, e.g. of glycolic acid and lactic acid. Moreover, liposome formulations which are known to the person skilled in the art (N. Weiner, Drug Develop Ind Pharm 15 (1989) 1523; "Liposome Dermatics, Springer Verlag 1992), for example HVJ liposomes (Hayashi, Gene Therapy 3 (1996) 878) are suitable. Dermal administration can be carried out, for example, also with the aid of ionophoretic methods and/or with the aid of electroporation. Moreover, lipofectins and/or other (nucleic acid or DNA) carrier systems, for example those which are used in gene therapy, can be used. In particular, suitable systems are those with whose aid oligonucleotides can be introduced into eukaryotic cells or the nuclei of eukaryotic cells with great efficiency.

In addition to the active compounds and vehicles, a pharmaceutical preparation can additionally contain additives, such as, for example, fillers, extenders, disintegrants, binding agents, lubricants, wetting agents, stabilizers, emulsifiers, preservatives, sweeteners, colorants, flavorings or aromatizers, thickening agents, diluents, buffer substances, furthermore solvents and/or solubilizers and/or agents for achieving a depot effect, and salts for changing the osmotic pressure, coating agents and/or antioxidants. They can also contain two or more different oligonucleotides and/or their physiologically tolerable salts and furthermore, in addition to at least one oligonucleotide, one or more other therapeutically active substances.

Examples

Example 1: Oligonucleotide synthesis

The oligonucleotide was synthesized on an automatic DNA synthesizer (Applied Biosystems Model 380B or 394) using the standard phosphoramidite chemistry and oxidation with iodine (F. Eckstein, Ed

"Oligonucleotides and Analogs, A Practical Approach", IRL Press, Oxford, 1991). For the introduction of phosphorothioate bridges in mixed phosphorothioates and phosphodiester oligonucleotide, oxidation was carried out with TETD (tetraethylthiuram disulfide) instead of iodine
 5 (Applied Biosystems User Bulletin 65). After removal of solid carrier (CPG or Tentagel) and removal of the protective groups with conc. NH_3 at 55°C (18 h), the oligonucleotide was first purified by butanol precipitation (Sawadogo, Van Dyke, Nucl. Acids Res. 19 (1991) 674). The sodium salt was then obtained by precipitation from a 0.5 M NaCl solution using
 10 2.5 parts by volume of ethanol.

The oligonucleotide was analyzed with the aid of

a) analytical gel electrophoresis (gel: 20% acrylamide, 8M urea; running
 15 buffer: 454M tris borate buffer, pH 7.0) and/or

b) HPLC analysis (column material: Waters GenPak FAX; gradient: CH_3CN (400 ml), H_2O (1.6 l), NaH_2PO_4 (3.1 g), NaCl (11.7 g) pH 6.8 (0.1 M in NaCl) after CH_3CN (400 ml), H_2O (1.6 l), NaH_2PO_4 (3.1 g), NaCl (175.3 g),
 20 pH 6.8 (1.5 M in NaCl)) and/or

c) capillary gel electrophoresis (Beckmann capillary eCAPTM, U100P gel column, 65 cm length, 100 mm I.D., window 15 cm from one end; buffer: 140 μM tris, 360 mM boric acid, 7M urea) and/or
 25

d) electrospray mass spectroscopy.

The analysis of the oligonucleotide showed that this was in each case present in a purity of greater than 90%. The methods for the analysis of
 30 oligonucleotides are described, for example, in Schweiber and Engler "Analysis of oligonucleotides" (in "Antisense – from technology to therapy", a laboratory manual and textbook, Schlingensiepen et al. eds., Biol. Science, Vol. 6 (1997) p. 78-103).

35 Synthesized oligonucleotide:

ODN1 (sequence SEQ ID NO. 24): 3'-GsGsAGGTsGGTsACsCsCsC-5'

Example 2: Production of a pharmaceutical preparation

50 mg of ODN 1 from Example 1 can be closely mixed with 1 g of Dermatop® (Hoechst Aktiengesellschaft, Frankfurt am Main, Germany) base cream and the mixture stored at temperatures of $<10^{\circ}\text{C}$.

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Example 3:

The cream from Example 2 can then be applied twice daily (in the morning and afternoon or evening) to a depigmented skin site of a vitiligo patient.

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Table 1: Sequence SEQ ID NO. 1:

Sequence of the human tenascin cDNA according to A. Siri et al. Nucl. Acids Res. 19 (1991) 525-531.

GAATTCGCTA GAGCCCTAGA GCGCCAGCAG CACCCAGCCA AACCCACCTC CACCATGGGG	60
GCCATGACTC AGCTGTTGGC AGGTGTCTTT CTTGCTTTCC TTGCCCTCGC TACCGAAGGT	120
GGGGTCTCTA AGAAAGTCAT CCGGCACAAG CGACAGAGTG GGGTGAACGC CACCCTGCCA	180
GAAGAGAACC AGCCAGTGGT GTTTAACCAC GTTTACAACA TCAAGCTGCC AGTGGGATCC	240
CAGTGTTCGG TGGATCTGGA GTCAGCCAGT GGGGAGAAAG ACCTGGCACC GCCTTCAGAG	300
CCCAGCGAAA GCTTTCAGGA GCACACACTA GATGGGGAAA ACCAGATTGT CTTACACAT	360
CGCATCAACA TCCCCCGCGG GGCCTGTGGC TGTGCCGCAG CCCCTGATGT TAAGGAGCTG	420
CTGAGCAGAC TGGAGGAGCT GGAGAACCCTG GTGTCTTCCC TGAGGGAGCA ATGTACTGCA	480
GGAGCAGGCT GCTGTCTCCA GCCTGCCACA GGCCGCTTGG ACACCAGGCC CTTCTGTAGC	540
GGTCGGGGCA ACTTCAGCAC TGAAGGATGT GGCTGTGTCT GCGAACCTGG CTGGAAGGCC	600
CCCAACTGCT CTGAGCCCGA ATGTCCAGGC AACTGTCACC TTCGAGGCCG GTGCATTGAT	660
GGGCAGTGCA TCTGTGACGA CGGCTTCACG GCGGAGGACT GCAGCCAGCT GGCTTGCCCC	720
AGCGACTGCA ATGACCAGGG CAAGTCCGTG AATGGAGTCT GCATCTGTTT CGAAGGCTAC	780
GCGGCTGACT GCAGCCGTGA AATCTGCCCA GTGCCCTGCA GTGAGGAGCA CGGCACATGT	840
GTAGATGGCT TGTGTGTGTG CCACGATGGC TTTCAGGGCG ATGACTGCAA CAAGCCTCTG	900
TGTCTCAACA ATTGCTACAA CCGTGGACGA TCGGTGGAGA ATGAGTGGCT GTCTGATGAC	960
GTTTTACGG GCGAAGACTG CAGTGAGCTC ATCTGCCCCA ATGACTGCTT CGACCGGGGC	1020
CGCTGCATCA ATGGCACCTG CTAATGCGAA GAAGGCTTCA CAGGTGAAGA CTGCGGGAAA	1080
CCCACCTGCC CACATGCCTG CCACACCCAG GGCCGGTGTG AGGAGGGGCA GTGTGTATGT	1140

GATGAGGGCT TTGCCGTGT GGAATGCAGC GAGAAGAGCT GTCCTGCTGA CTGTCAACAAT	1200
CGTGGCGGCT GTGTAGACGG GCGGTGTGAG TGTGATGATG GTTTCAGTGG AGCTGACTGT	1260
GGGGAGCTCA AGTGTCCCAA TGGCTGCAGT GGCCATGGCC GCTGTGTCAA TGGGCAGTGT	1320
GTGTGTGATG AGGGCTATAC TGGGGAGGAC TGCAGCCAGC TACGGTGCCC CAATGACTGT	1380
CACAGTCGGG GCCGCTGTGT CCAGGGGCAA TGTGTATGTG AGCAAGGCTT CAAGGGCTAT	1440
GACTGCAGTG ACATGAGCTG CCCTAATGAC TGTACCAGC ACGGCCGCTG TGTGAATGGC	1500
ATGTGTGTTT GTGATGACGG CTACACAGGG GAAGACTGCC GGGATCGCCA ATGCCCCAGG	1560
GACTGCAGCA ACAGGGGCTT CTGTGTGGAC GGACAGTGCG TCTGTGAGGA CGGCTTCACC	1620
GGCCCTGACT GTGCAGAACT CTCCTGTCCA AATGACTGCC ATGGCCAGGG TCGCTGTGTG	1680
AATGGGCACT GCGTGTGCCA TGAAGGATTT ATGGGCAAAG ACTGCAAGGA GCAAAGATGT	1740
CCCAGTCACT GTCATGGCCA GGGCCGCTGC GTGGACGGCC AGTGCACTCTG CCACGAGGGC	1800
TTACACAGGC TGGACTGTGG CCAGCACTCC TGCCCCAGTG ACTGCAACAA CTTAGGACAA	1860
TGCGTCTCGG GCCGCTGCAT CTGCAACGAG GGCTACAGCG GAGAAGACTG CTCAGAGGTG	1920
TCTCCTCCCA AAGACCTCGT TGTGACAGAA GTGACGGAAG AGACGGTCAA CCTGGCCTGG	1980
GACAATGAGA TGCGGGTCAC AGAGTACCTT GTCGTGTACA CCCCCACCA CGAGGGTGGT	2040
CTGGAAATGC AGTTCGGTGT GCCTGGGGAC CAGACGTCCA CCATCATCCG GGAGCTGGAG	2100
CCTGGTGTGG AGTACTTTAT CCGTGTATTT GCCATCCTGG AGAACAAGAA GAGCATTCTT	2160
GTCAGCGCCA GGGTGGCCAC GTACTTACCT GCACCTGAAG GCCTGAAATT CAAGTCCATC	2220
AAGGAGACAT CTGTGGAAGT GGAGTGGGAT CCTCTAGACA TTGCTTTTGA AACCTGGGAG	2280
ATCATCTTCC GGAATATGAA TAAAGAAGAT GAGGGAGAGA TCACCAAAAG CCTGAGGAGG	2340
CCAGAGACCT CTTACCGGCA AACTGGTCTA GCTCCTGGGC AAGAGTATGA GATATCTCTG	2400
CACATAGTGA AAAACAATAC CCGGGGCCCT GGCCTGAAGA GGGTGACCAC CACACGCTTG	2460

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GATGCCCCCA GCCAGATCGA GGTGAAAGAT GTCACAGACA CCACTGCCTT GATCACCTGG	2520
TTCAAGCCCC TGGCTGAGAT CGATGGCATT GAGCTGACCT ACGGCATCAA AGACGTGCCA	2580
GGAGACCGTA CCACCATCGA TCTCAGAG GACGAGAACC AGTACTCCAT CGGGAACCTG	2640
AAGCCTGACA CTGAGTACGA GGTGTCCCTC ATCTCCCGCA GAGGTGACAT GTCAAGCAAC	2700
CCAGCCAAAG AGACCTTCAC AACAGGCCTC GATGCTCCCA GGAATCTTCG ACGTGTTC	2760
CAGACAGATA ACAGCATCAC CCTGGAATGG AGGAATGGCA AGGCAGCTAT TGACAGTTAC	2820
AGAATTAAGT ATGCCCCCAT CTCTGGAGGG GACCACGCTG AGTTGATGT TCCAAAGAGC	2880
CAACAAGCCA CAACCAAAC CACACTCACA GGTCTGAGGC CGGGAACCTGA ATATGGGATT	2940
GGAGTTTCTG CTGTGAAGGA AGACAAGGAG AGCAATCCAG CGACCATCAA CGCAGCCACA	3000
GAGTTGGACA CGCCCAAGGA CCTTCAGGTT TCTGAAACTC CAGAGACCAG CCTGACCTG	3060
CTCTGGAAGA CACCGTTGGC CAAATTTGAC CGCTACCGCC TCAATTACAG TCTCCCCACA	3120
GGCCAGTGGG TGGGAGTGCA GCTTCCAAGA AACACCACTT CCTATGTCTT GAGAGGCCTG	3180
GAACCAGGAC AGGAGTACAA TGTCTCTCTG ACAGCCGAGA AAGGCAGACA CAAGAGCAAG	3240
CCCGCACGTG TGAAGGCATC CACTGAACAA GCCCCTGAGC TGGAAAACCT CACCGTGACT	3300
GAGGTTGGCT GGGATGGCCT CAGACTCAAC TGGACCGGG CTGACCAGGC CTATGAGCAC	3360
TTTATCATTC AGGTGCAGGA GGCCAACAAG GTGGAGGCAG CTCGGAACCT CACCGTGCCT	3420
GGCAGCCTTC GGGCTGTGGA CATACCGGGC CTCAGGCTG CTACGCCTTA TACAGTCTCC	3480
ATCTATGGGG TGATCCAGGG CTATAGAACA CCACTGCTCT CTGCTGAGGC CTCCACAGGG	3540
GAAACTCCCA ATTTGGGAGA GGTCTGGTG GCCGAGGTGG GCTGGGATGC CCTCAAACCTC	3600
AACCTGACTG CTCCAGAAGG GGCCTATGAG TACTTTTCA TTCAGGTGCA GGAGGCTGAC	3660
ACAGTAGAGG CAGCCCAGAA CCTCACCGTC CCAGGAGGAC TGAGGTCCAC AGACCTGCCT	3720
GGGCTCAAAG CAGCCACTCA TTATACCATC ACCATCCGG GGGTCACTCA GGACTTCAGC	3780

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ACAACCCCTC TCTCTGTTGA AGTCTTGACA GAGGAGGTTT CAGATATGGG AAACCTCACA 3840
 GTGACCGAGG TTAGCTGGGA TGCTCTCAGA CTGAAGTGGG CCACGCCAGA TGGAACCTAT 3900
 GACCAGTTTA CTATTCAGGT CCAGGAGGCT GACCAGGTTG AAGAGGCTCA CAATCTCACC 3960
 GTTCCTGGCA GCCTGCGTTC CATGGAAATC CCAGGCCTCA GGGCTGGCAC TCCTTACACA 4020
 GTCACCCTGC ACGGCCAGGT CAGGGGCCAC AGCACTCGAC CCCTTGCTGT AGAGGTCGTC 4080
 CAGTGGGACG TGCCGCTCCA GTCCCGGTG TCGTGAGCTG GGAACGACA TCTCCAGCAG 4140
 ACAGAGGATC TCCACAGCT GGGAGATTGA GCCGTGTCTG AGGTTGGCTG GGATGGCCTC 4200
 AGACTCAACT GGACCGCAGC TGACAATGCC TATGAGCACT TTGTCATTCA GGTGCAGGAG 4260
 GTCAACAAAG TGGAGGCAGC CCAGAACCTC ACGTTGCCTG GCAGCCTCAG GGCTGTGGAC 4320
 ATCCCGGGCC TCGAGGCTGC CACGCCTTAT AGAGTCTCCA TCTATGGGGT GATCCGGGGC 4380
 TATAGAACAC CAGTACTCTC TGCTGAGGCC TCCACAGCCA AAGAACCTGA AATTGGAAC 4440
 TTAAATGTTT CTGACATAAC TCCCGAGAGC TTCAATCTCT CCTGGATGGC TACCGATGGG 4500
 ATCTTCGAGA CCTTTACCAT TGAAATTATT GATTCCAATA GGTTCCTGGA CACTGTGGAA 4560
 TATAATATCT CTGGTGCTGA ACCAACTGCC CATATCTCAG GGCTACCCCC TAGTACTGAT 4620
 TTTATTGTCT ACCTCTCTGG ACTTGCTCCC AGCATCCGGA CCAAAACCAT CAGTGCCACA 4680
 GCCACGACAG AGGCCCTGCC CTTTCTGGAA AACCTAACCA TTTCCGACAT TAATCCCTAC 4740
 GGGTTCACAG TTTCTGGAT GGCATCGGAG AATGCCTTTG ACAGCTTTCT AGTAACGGTG 4800
 GTGGATTCTG GGAAGCTGCT GGACCCCCAG GAATTCACAC TTTCAGGAAC CCAGAGGAAC 4860
 CTGGAGCTTA GAGGCCTCAT AACTGGCATT GGCTATGAGG TTATGGTCTC TGGCTTCACC 4920
 CAAGGGCATC AAACCAAGCC CTTGAGGCT GAGATTGTTA CAGAAGCCGA ACCGGAAGTT 4980
 GACAACCTTC TGTTTTAGA TGCCACCCCA GACGGTTTCC GTCTGTCTG GACAGCTGAT 5040
 GAAGGGGTCT TCGACAATTT TGTCTCAAA ATCAGAGATA CCAAAAAGCA GTCTGAGCCA 5100

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CTGGAAATAA CCCTACTTGC CCCCGAACGT ACCAGGGACA TAACAGGTCT CAGAGAGGCT 5160
 ACTGAATACG AAATTGAACT CTATGGAATA AGCAAAGGAA GCGCATCCCA GACAGTCAGT 5220
 GCTATAGCAA CAACAGCCAT GGGCTCCCCA AAGGAAGTCA TTTTCTCAGA CATCACTGAA 5280
 AATTGGGCTA CTGTCAGCTG GAGGGCACCC ACGGCCCAAG TGGACAGCTT CCGGATTACC 5340
 TATGTGCCCCA TTACAGGAGG TACACCTCC ATGGTAACTG TGGACGGAAC CAAGACTCAG 5400
 ACCAGGCTGG TGAAACTCAT ACCTGGCGTG GAGTACCTTG TCAGCATCAT CGCCATGAAG 5460
 GGCTTTGAGG AAAGTGAACC TGTCTCAGGG TCATTACCA CAGCTCTGGA TGGCCCATCT 5520
 GGCCTGGTGA CAGCCAACAT CACTGACTCA GAAGCCTTGG CCAGGTGGCA GCCAGCCATT 5580
 CCCACTGTGG ACAGTTATGT CATCTCTAC ACAGGCGAGA AAGTGCCAGA AATTACCGC 5640
 ACGGTGTCCG GGAACACAGT GGAGTATGCT CTGACCGACC TCGAGCCTGC CACGGAATAC 5700
 ACACTGAGAA TCTTTGCAGA GAAAGGGCCC CAGAAGAGCT CAACCATCAC TGCCAAGTTC 5760
 ACAACAGACC TCGATTCTCC AAGAGACTTG ACTGCTACTG AGGTTCACTC GGAAACTGCC 5820
 CTCCTTACCT GCGGACCCCC CCGGGCATCA GTCACCGGT ACCTGCTGGT CTATGAATCA 5880
 GTGGATGGCX CAGTCAAGGA AGTCATTGTG GGTCCAGATA CCACCTCCTA CAGCCTGGCA 5940
 GACCTGAGCC CATCCACCCA CTACACAGCC AAGATCCAGG CACTCAATGG GCCCCTGAGG 6000
 AGCAATATGA TCCAGACCAT CTTCAACCACA ATTGGACTCC TGTACCCCTT CCCCAGGCAC 6060
 TGCTCCCAAG CAATGCTGAA TGGAGACAGG ACCTCTGGCC TCTACACCAT TTATCTGAAT 6120
 GGTGATAAGC CTCAGGCGCT GGAAGTCTTC TGTGACATGA CCTCTGATGG GGGTGGATGG 6180
 ATTGTGTTCC TGAGACGCAA AAACGGACGC GAGAATTCT ACCAAAAGTG GAAGGCATAT 6240
 GCTGCTGGAT TTGGGGACCG CAGAGAAGAA TTCTGGCTTG GCTTGGACAA CCTGAACAAA 6300
 ATCAGAGCCC AGGGGCAGTA CGAGCTCCGG GTGGACCTGC GGGACCATGG GGAGACAGCC 6360
 TTGCTGTCT ATGACAAGT CAGCGTGGGA GATGCCAAGA CTCGCTACAA GCTGAAGGTC 6420

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GAGGGGTACA GTGGGACAGC AGGTGACTCC ATCGCCTACC ACAATGGCAG ATCCTTCTCC	6480
ACCTTTGACA AGGACACAGA TTCAGCCATC ACCAACTGTG CTCTGTCTAC AAGGGGCTTC	6540
TGGTACAGGA ACTGTCACCG TGTCAACCTG ATGGGGAGAT ATGGGGACAA TAACCACAGT	6600
CAGGGCGTTA ACTGGTTCCA CTGGAAGGGC CACGAACACT CAATCCAGTT TGCTGAGATG	6660
AAGCTGAGAC CAAGCAACTT CAGAAATCTT GAAGGCAGGC GCAAACGGGC ATAAATTGGA	6720
GGGACCACTG GGTGAGAGAG GAATAAGGCC GCCCAGAGCG AGGAAAGGAT TTTACCAAG	6780
CATCAATACA ACCAGCCCAA CCATCGGTCC ACACCTGGGC ATTTGGTGAG AATCAAAGCT	6840
GACCATGGAT CCCTGGGGCC AACGGCAACA GCATGGGCCT CACCTCCTCT CTGATTTCTT	6900
TCTTTGCACC AAAGACATCA GTCTCCAACA TCTTTCTGTT TTGTTGTTTG ATTCAGCAAA	6960
AATCTCCCAG TGACAACATC GCAATAGTTT TTTACTTCTC TTAGGTGGCT CTGGGATGGG	7020
AGAGGGGTAG GATGTACAGG GGTAGTTTGT TTTAGAACCA GCCGTATTTT ACATGAAGCT	7080
GTATAATTAA TTGTCATTAT TTTTGTAGC AAAGATTAAA TGTGTCATTG GAAGCCATCC	7140
CTTTTTTTAC ATTTCAATCA ACAGAAACCA GAAAAGCAAT ACTGTTTCCA TTTTAAGGAT	7200
ATGATTAATA TTATTAAATAT AATAATGATG ATGATGATGA TGAAAACTAA GGATTTTICA	7260
ACAGATCTTT CTTTCCAAA CATTTCGGA CAGTACCTGA TTGTATTTT TTTTAAATA	7320
AAAGCACAAG TACTTTTGAA AAAAAA	7346

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Patent claims:

1. An oligonucleotide which binds to a nucleic acid which codes for one of the isoforms of human tenascin or parts thereof and inhibits its expression, where the oligonucleotide has a length of 7 to 15 nucleotide units and where the oligonucleotide can optionally be modified, and the physiologically tolerable salts of the oligonucleotide.
2. The oligonucleotide as claimed in claim 1, in which the oligonucleotide binds to a region of the nucleic acid which comprises
 - a) a part of the 5'-noncoding region and/or the translation start or
 - b) the translation start and/or a part of the coding region or
 - c) a part of the coding region and/or a part of the 3'-noncoding region.
3. The oligonucleotide as claimed in claim 1, in which the oligonucleotide has one of the sequences SEQ ID NO. 2 to SEQ ID NO. 20, where SEQ ID NO. 2 to SEQ ID NO. 20 have the following meaning:

SEQ. ID NO. 2: 3'-GGTTTGGGTGGAGGTGG-5'

SEQ. ID NO. 3: 3'-GGAGGTGGTACCCCCGG-5'

SEQ. ID NO. 4: 3'-GGTGGTACCCCCGG-5'

SEQ. ID NO. 5: 3'-GGAGGTGGTACCCC-5'

SEQ. ID NO. 6: 3'-AGAAAGAACGAAAGGAA-5'

SEQ. ID NO. 7: 3'-GGAGGTGGTACC-5'

SEQ. ID NO. 8: 3'-GGAGCGATGGCTTCCA-5'

SEQ. ID NO. 9: 3'-AAAGGAACGGGAGCG-5'

SEQ. ID NO. 10: 3'-GGTCGGTTTGGGTGG-5'

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SEQ. ID NO. 11: 3'-CTTACAGGTCCGTTGA -5'
 SEQ. ID NO. 12: 3'-GGCCGTGTTGCTGT -5'
 SEQ. ID NO. 13: 3'-TCACCCCTCTTTCTGG -5'
 SEQ. ID NO. 14: 3'-GGACACCGACACGG -5'
 SEQ. ID NO. 15: 3'-AACGGGAGCGATGG -5'
 SEQ. ID NO. 16: 3'-ATCTCGGGGTCGTC -5'
 SEQ. ID NO. 17: 3'-AAAGAACGAAAGGAA -5'
 SEQ. ID NO. 18: 3'-GGTGGTACCCC -5'
 SEQ. ID NO. 19: 3'-CCCGGTACTGA -5'
 SEQ. ID NO. 20: 3'-CCACAGAAAGAAC -5'

4. The oligonucleotide as claimed in one or more of claims 1 to 3, in which the oligonucleotide has one or more modifications which are located on certain nucleoside positions and/or internucleoside bridges.

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5. The oligonucleotide as claimed in one or more of claims 1 to 4, in which the chemical modifications can be selected independently of one another from the group consisting of the chemical modifications a) to h):
- a) the replacement of a phosphoric acid diester internucleoside bridge by a modified phospho bridge,
 - 10 b) the replacement of a phosphoric acid diester internucleoside bridge by a "dephospho" bridge,
 - c) the replacement of a sugar phosphate unit by another unit,
 - d) the replacement of a β -D-2'-deoxyribose unit by a modified sugar unit,
 - 15 e) the modification or the replacement of a natural nucleoside base by a modified nucleoside base,
 - f) the conjugation of the oligonucleotide to a molecule which adapts the properties of the oligonucleotide to a specific requirement,
 - g) the conjugation of the oligonucleotide to a 2'5'-bonded oligoadenylate or a derivative thereof, the conjugation of the 2'5'-bonded oligoadenylate or a derivative thereof optionally taking place via a linker,
 - 20 and
 - h) the introduction of a 3'-3' inversion and/or 5'-5' inversion at the 3' or 5' end of the oligonucleotide.

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6. The oligonucleotide as claimed in one or more of claims 1 to 5, the oligonucleotide containing one or more chemical modifications which can be selected independently of one another from the group consisting of the chemical modifications a) to h):

a) the replacement of a phosphoric acid diester internucleoside bridge by a modified phospho bridge,

where a modified phospho bridge is a phosphorothioate, phosphorodithioate, $\text{NR}^1\text{R}^{1'}$ -phosphoramidate, boranophosphate, phosphate-($\text{C}_1\text{-C}_{21}$)-O-alkyl ester, phosphate-[($\text{C}_6\text{-C}_{12}$)aryl-($\text{C}_1\text{-C}_{21}$)-O-alkyl] ester, ($\text{C}_1\text{-C}_8$)alkylphosphonate or ($\text{C}_6\text{-C}_{12}$)-arylphosphonate bridge,

where

R^1 and $\text{R}^{1'}$ independently of one another are selected from the group comprising hydrogen, ($\text{C}_1\text{-C}_{18}$)-alkyl, ($\text{C}_6\text{-C}_{20}$)-aryl, ($\text{C}_6\text{-C}_{14}$)-aryl-($\text{C}_1\text{-C}_8$)-alkyl or

R^1 and $\text{R}^{1'}$ together with the nitrogen atom carrying them, form a 5- to 6-membered heterocyclic ring which can additionally contain a further heteroatom from the group consisting of O, S and N;

b) the replacement of a phosphoric acid diester internucleoside bridge by a "dephospho" bridge,

where a "dephospho bridge" is a formacetal, 3'-thioformacetal, methylhydroxylamine, oxime, methylenedimethylhydrazo, dimethylenesulfone or silyl bridge,

c) the complete or partial replacement of the sugar phosphate backbone (replacement of sugar phosphate units) by other units,

where another unit is suitable for synthesizing a "morpholine derivative" oligomer, a polyamide nucleic acid ("PNA") or a phosphomonoacid ester nucleic acid,

d) the replacement of a β -D-2'-deoxyribose unit by a modified sugar unit,

where a modified sugar unit is an α -D-2'-deoxyribose, L-2'-deoxyribose, 2'-F-2'-deoxyribose, 2'-O-($\text{C}_1\text{-C}_6$)alkylribose, 2'-O-($\text{C}_2\text{-C}_6$)alkenylribose, 2'-[O-($\text{C}_1\text{-C}_6$)alkyl-O-($\text{C}_1\text{-C}_6$)alkyl]ribose, 2'- NH_2 -2'-deoxyribose, β -D-xylofuranose, α -arabinofuranose, 2,4-dideoxy- β -D-erythro-hexopyranose, a carbocyclic sugar analog, an open-chain sugar analog or a bicyclo sugar analog,

e) the replacement of a natural nucleoside base by a modified nucleoside base,

where a modified nucleoside base is 5-(hydroxymethyl)uracil, 5-aminouracil, pseudouracil, dihydrouracil, 5-($\text{C}_1\text{-C}_6$ -alkyl)uracil, 5-($\text{C}_2\text{-C}_6$)-alkenyluracil, 5-($\text{C}_2\text{-C}_6$)-alkynyluracil, 5-($\text{C}_1\text{-C}_6$)-alkylcytosine, 5-($\text{C}_2\text{-C}_6$)-alkenylcytosine, 5-($\text{C}_2\text{-C}_6$)-alkynylcytosine, 5-fluorouracil, 5-fluorocytosine, 5-chlorouracil, 5-chlorocytosine, 5-bromouracil, 5-

f) conjugation to a molecule,

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7. The oligonucleotide as claimed in one or more of claims 1 to 6, in which either

- a) only certain phosphodiester internucleoside bridges or
- b) all phosphodiester internucleoside bridges

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are modified.

8. The oligonucleotide as claimed in one or more of claims 1 to 7, in which 1 – 5 terminal internucleoside bridges are modified at the 5- and/or at the 3'- end of the oligonucleotide.

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9. The oligonucleotide as claimed in one or more of claims 1 to 8, in which the internucleoside bridges located at the 3'- and/or 5'- end of nonterminal nucleosides which contain a pyrimidine base are modified.

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10. The oligonucleotide as claimed in one or more of claims 1 to 9, in which the oligonucleotide has a sequence selected from the group consisting of the sequences SEQ ID NO. 21 to SEQ ID NO. 39, the sequences SEQ ID NO. 21 to SEQ ID NO. 39 having the following meaning:

- SEQ ID NO. 21: 3'-GsGsTsTsTGGGTsGGAGGsTsGsG -5',
 SEQ ID NO. 22: 3'-GsGsAsGGTsGGTACsCCsCCsGsG -5',
 SEQ ID NO. 23: 3'-GsGsTGGTACsCsCCsCsGsG -5',
 SEQ ID NO. 24: 3'-GsGsAGGTsGGTACsCsCsC -5',
 SEQ ID NO. 25: 3'-AsGsAAAGAAcCsGAAAGGsAsA -5',
 SEQ ID NO. 26: 3'-GsGsAGGTsGGTAsCsC -5',
 SEQ ID NO. 27: 3'-GsGsAGCsGATsGGCsTsTsCsCsA -5',
 SEQ ID NO. 28: 3'-AsAsAGGAACsGGGAGsCsG -5',
 SEQ ID NO. 29: 3'-GsGsTCGGTsTsTGGGTsGsG -5',
 SEQ ID NO. 30: 3'-CsTsTACAGGTsCsCGTsTsGsA -5',
 SEQ ID NO. 31: 3'-GsGsCsCGsTGTsTCGCsTsGsT -5',
 SEQ ID NO. 32: 3'-TsCsACsCCsCTsCsTTsTsCsTsGsG -5',
 SEQ ID NO. 33: 3'-GsGsAsCACsCGACsACsGsG -5',
 SEQ ID NO. 34: 3'-AsAsCsGGGAGCGATsGsG -5',
 SEQ ID NO. 35: 3'-AsTsCsTCGGGGTsCsGsTsC -5',
 SEQ ID NO. 36: 3'-AsAsAGAACsGAAAGGsAsA -5',
 SEQ ID NO. 37: 3'-GsGsTGGTACsCsCsC -5',
 SEQ ID NO. 38: 3'-CsCsCsGGTACsTsGsA -5' and
 SEQ ID NO. 39: 3'-CsCsAsCAGAAAGsAsAsC -5',

where "s" indicates the position of a modified internucleoside bridge.

- 5 11. The oligonucleotide as claimed in one or more of claims 1 to 8, where the oligonucleotide has one of the sequences SEQ ID NO. 40 to SEQ ID NO. 58, the sequences SEQ ID NO. 40 to SEQ ID NO. 58 having the following meaning

- SEQ ID NO. 40: 3'- GyGyTyTyTyGxGxGxTxGxGxAxGyGyTyGyG -5',
 SEQ ID NO. 41: 3'- GyGyAyGyGyTxGxGxTxAxCxCxCyCyCyGyG -5',
 SEQ ID NO. 42: 3'- GyGyTxGxGxTxAxCxCxCxCyCyGyG -5',
 SEQ ID NO. 43: 3'- GyGyAyGyGxTxGxGxTxAxCyCyCyC -5',
 SEQ ID NO. 44: 3'- AyGyAyAxAxGxAxAxCxGxAxAxGyGyAyA -5',
 SEQ ID NO. 45: 3'- GyGyAxGxGxTxGxGxTxAyCyC -5',
 SEQ ID NO. 46: 3'- GyGyAxGxCxGxAxTxGyGyCyTyTyCyCyA -5',
 SEQ ID NO. 47: 3'- AyAyAyGxGxAxAxCxGxGyGyAyGyCyG -5',
 SEQ ID NO. 48: 3'- GyGyTyCxGxGxTxTxTxGxGyGyTyGyG -5',
 SEQ ID NO. 49: 3'- CyTyTyAxCxAxGxGxTxCxCxGyTyTyGyA -5',
 SEQ ID NO. 50: 3'- GyGyCyCxGxTxGxTxTxCxGyCyTyGyT -5',
 SEQ ID NO. 51: 3'- TyCyAyCxCxCxTxTxTxTyTyCyTyGyG -5',
 SEQ ID NO. 52: 3'- GyGyAyCxAxCxCxGxAxCxAyCyGyG -5',
 SEQ ID NO. 53: 3'- AyAyCyGxGxGxAxGxCxGxAyTyGyG -5',
 SEQ ID NO. 54: 3'- AyTyCyTxCxGxGxGxTxCxGyTyC -5',
 SEQ ID NO. 55: 3'- AyAyAyGxAxAxCxGxAxAxGyGyAyA -5',
 SEQ ID NO. 56: 3'- GyGyTxGxGxTxAxCxCyCyC -5',
 SEQ ID NO. 57: 3'- CyCxCxGxGxTxAxCyTyGyA -5' and
 SEQ ID NO. 58: 3'- CyCyAxCxAxGxAxAxGyAyAyC -5',

where

- "x" independently of one another represents a phosphodiester
 internucleoside bridge or a modified internucleoside bridge and
 "y" independently of one another represents the replacement of a sugar
 phosphate unit or of a β -D-2'-deoxyribose unit, the modified β -D-2'-
 deoxyribose unit being located at the 3'- end of "y".

12. The oligonucleotide as claimed in claim 11, where "y" represents 2'-
 O-methyl-, 2'-O-propyl- or 2'-methoxyethoxyribose or a PNA unit.
13. The use of an oligonucleotide as claimed in one or more of claims 1
 to 12 for the inhibition of the expression of tenascin.
14. The use of an oligonucleotide as claimed in one or more of claims 1
 to 12 as a tool in molecular biology.

15. The use of an oligonucleotide as claimed in one or more of claims 1 to 12 as a diagnostic.
16. The use of an oligonucleotide as claimed in one or more of claims 1 to 12 as a pharmaceutical.
17. The use of an oligonucleotide as claimed in one or more of claims 1 to 12 for the production of a pharmaceutical.
18. A pharmaceutical comprising one or more oligonucleotides as claimed in one or more of claims 1 to 12 and, if appropriate, one or more pharmaceutical vehicles and/or additives.
19. The use of a pharmaceutical as claimed in claim 18 in combination with photochemotherapy and/or the transplantation of cultured melanocytes and/or treatment with steroids and/or treatment with placenta extracts.
20. A process for the production of a pharmaceutical, an efficacious dose of one or more oligonucleotides as claimed in one or more of claims 1 to 12 being mixed with one or more pharmaceutical vehicles and/or additives.
21. A process for the preparation of an oligonucleotide as claimed in one or more of claims 1 to 12, the oligonucleotide being chemically synthesized on a solid phase.
22. A diagnostic comprising one or more oligonucleotides as claimed in one or more of claims 1 to 12.
23. A test kit comprising one or more oligonucleotides as claimed in one or more of claims 1 to 12.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

As below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below, I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Antisense oligonucleotides against tenascin for the treating of vitiligo

the specification of which

was filed on October 29, 1998 as International Patent Application PCT/EP98/06868.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s) for which Priority is Claimed:

Federal Republic of Germany, 19750702.6-44 of NOVEMBER 15, 1997

And I hereby appoint

Douglas B. Henderson, Reg.No. 20,291; Arthur S. Garrett, Reg.No. 20,338
Jerry D. Voight, Reg.No. 23,020; Herbert H. Mintz, Reg.No. 26,691;
Thomas L. Irving, Reg.No. 28,619; Thomas W. Winland, Reg.No. 27,605;
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M. Paul Barker, Reg.No. 32,013; Charles E. Van Horn, Reg.No. 40,266;
David S. Forman, Reg.No. 33,694;

all of the firm of FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, Reg.No. 22,540, my attorneys, with full power of substitution and revocation to prosecute this application, to make alterations and amendments therein, to file continuation and divisional applications thereof, to receive the Patent, and to transact all business in the Patent and Trademark Office and in the Courts in connection therein, and specify that communications about the application are to be directed to the following correspondence address:

FINNEGAN, HENDERSON, FARABOW, GARRETT AND DUNNER
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00446 494960

HMR 1997/L238 US PCT

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

INVENTOR(S) / Residence

- 1 - 00 1) Dr. Anuschirwan Peyman, Zeilsheimer Straße 46, 65779 Kelkheim, Germany DEX

Signature: 

Date: 23.5.2000

- 2 - 00 2) Dr. Eugen Uhlmann, Zum Talblick 31, 61479 Glashütten, Germany DEX

Signature: 

Date: 23.5.2000

- 3 - 00 3) Caroline Weiser, Karl-Staib-Straße 37, 65795 Hattersheim, Germany DEX

Signature: 

Date: 09.06.2000

The inventors are citizens of Germany.

Post Office Address of all Inventors:

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: Hoechst Marion Roussel Deutschland GmbH
(B) STREET: -
(C) CITY: Frankfurt
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(E) COUNTRY: Germany
(F) POSTAL CODE (ZIP): 65926
(G) TELEPHONE: 069-305-7072
(H) TELEFAX: 069-35-7175
(I) TELEX: -

(ii) TITLE OF INVENTION: Antisense Oligonukleotide gegen Tenascin zur
Behandlung von Vitiligo

(iii) NUMBER OF SEQUENCES: 58

(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 7346 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: exon
(B) LOCATION: 1..7346

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

GAATTCGCTA	GAGCCCTAGA	GCCCCAGCAG	CACCCAGCCA	AACCCACCTC	CACCATGGGG	60
GCCATGACTC	AGCTGTTGGC	AGGTGTCTTT	CTTGCTTTCC	TTGCCCTCGC	TACCGAAGGT	120
GGGGTCCTCA	AGAAAGTCAT	CCGGCACAAG	CGACAGAGTG	GGGTGAACGC	CACCTGCCA	180
GAAGAGAACC	AGCCAGTGGT	GTTTAACCAC	GTTTACAACA	TCAAGCTGCC	AGTGGGATCC	240
CAGTGTTTCG	TGGATCTGGA	GTCAGCCAGT	GGGGAGAAAG	ACCTGGCACC	GCCTTCAGAG	300
CCCAGCGAAA	GCTTTCAGGA	GCACACAGTA	GATGGGGAAA	ACCAGATTGT	CTTCACACAT	360
CGCATCAACA	TCCCCCGCCG	GGCCTGTGGC	TGTGCCGCAG	CCCCTGATGT	TAAGGAGCTG	420
CTGAGCAGAC	TGGAGGAGCT	GGAGAACCTG	GTGTCTTCCC	TGAGGGAGCA	ATGTACTGCA	480
GGAGCAGGCT	GCTGTCTCCA	GCCTGCCACA	GGCCGCTTGG	ACACCAGGCC	CTTCTGTAGC	540
GGTCGGGGCA	ACTTCAGCAC	TGAAGGATGT	GGCTGTGTCT	GCGAACCTGG	CTGGAAAGGC	600
CCCAACTGCT	CTGAGCCCCG	ATGTCCAGGC	AACTGTCACC	TTGAGGCCCG	GTGCATTGAT	660
GGGCAGTGCA	TCTGTGACGA	CGGCTTCACG	GGCGAGGACT	GCAGCCAGCT	GGCTTGCCCC	720
AGCGACTGCA	ATGACCAGGG	CAAGTGCGTG	AATGGAGTCT	GCATCTGTTT	CGAAGGCTAC	780
GCGGCTGACT	GCAGCCGTGA	AATCTGCCCA	GTGCCCTGCA	GTGAGGAGCA	CGGCACATGT	840
GTAGATGGCT	TGTGTGTGTG	CCACGATGGC	TTTGCAGGCG	ATGACTGCAA	CAAGCCTCTG	900
TGTCTCAACA	ATTGCTACAA	CCGTGGACGA	TGCGTGGAGA	ATGAGTGCCT	GTGTGATGAG	960

REPLACEMENT SHEET (RULE 26)

GGTTTCACGG	GCGAAGACTG	CAGTGAGCTC	ATCTGCCCCA	ATGACTGCTT	CGACCGGGGC	1020
CGCTGCATCA	ATGGCACCTG	CTACTGCGAA	GAAGGCTTCA	CAGGTGAAGA	CTGCGGGAAA	1080
CCCACCTGCC	CACATGCCTG	CCACACCCAG	GGCCGGTGTG	AGGAGGGGCA	GTGTGTATGT	1140
GATGAGGGCT	TTGCCGGTGT	GGACTGCAGC	GAGAAGAGGT	GTCCTGCTGA	CTGTCACAAT	1200
CGTGGCCGCT	GTGTAGACGG	GCGGTGTGAG	TGTGATGATG	GTTTCACTGG	AGCTGACTGT	1260
GGGGAGCTCA	AGTGTCCCAA	TGGCTGCAGT	GGCCATGGCC	GCTGTGTCAA	TGGGCAGTGT	1320
GTGTGTGATG	AGGGCTATAC	TGGGGAGGAC	TGCAGCCAGC	TACGGTGCCC	CAATGACTGT	1380
CACAGTCGGG	GCCGCTGTGT	CGAGGGCAAA	TGTGTATGTG	AGCAAGGCTT	CAAGGGCTAT	1440
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CCCAGTGACT	GTGATGGCCA	GGGCCGCTGC	GTGGACGGCC	AGTGCATCTG	CCACGAGGGC	1800
TTCACAGGCC	TGGACTGTGG	CCAGCACTCC	TGCCCCAGTG	ACTGCAACAA	CTTAGGACAA	1860
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GACAAATGAGA	TGCGGGTCAC	AGAGTACCTT	GTCGTGTACA	CGCCACCCA	CGAGGGTGGT	2040
CTGGAATGC	AGTTCCGTGT	GCCTGGGGAC	CAGACGTCCA	CCATCATCCG	GGAGCTGGAG	2100
CCTGGTGTGG	AGTACTTTAT	CCGTGTATTT	GCCATCTTGG	AGAACAAGAA	GAGCATTCCT	2160
GTCAGCGCCA	GGGTGGCCAC	GTACTTACCT	GACCTGAAG	GCCTGAAATT	CAAGTCCATC	2220
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ATCATCTTCC	GGAATATGAA	TAAAGAAGAT	GAGGGAGAGA	TCACCAAAAG	CCTGAGGAGG	2340
CCAGAGACCT	CTTACCGGCA	AACCTGGTCTA	GCTCCTGGGC	AAGAGTATGA	GATATCTCTG	2400
CACATAGTGA	AAAACAATAC	CCGGGGCCCT	GGCCTGAAGA	GGGTGACCAC	CACACGCTTG	2460
GATGCCCCCA	GCCAGATCGA	GGTGAAAGAT	GTCACAGACA	CCACTGCCTT	GATCACCTGG	2520
TTCAAGCCCC	TGGCTGAGAT	CGATGGCATT	GAGCTGACCT	ACGGCATCAA	AGACGTGCCA	2580
GGAGACCGTA	CCACCATCGA	TCTCACAGAG	GACGAGAACC	AGTACTCCAT	CGGGAACCTG	2640
AAGCCTGACA	CTGAGTACGA	GGTGTCCCTC	ATCTCCCGCA	GAGGTGACAT	GTCAAGCAAC	2700
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CAGACAGATA	ACAGCATCAC	CCTGGAATGG	AGGAATGGCA	AGGCAGCTAT	TGACAGTTAC	2820
AGAATTAAAGT	ATGCCCCCAT	CTCTGGAGGG	GACCACGCTG	AGGTTGATGT	TCCAAAGAGC	2880
CAACAAGCCA	CAACCAAAAC	CACACTCACA	GGTCTGAGGC	CGGGAAGTGA	ATATGGGATT	2940
GGAGTTTCTG	CTGTGAAGGA	AGACAAGGAG	AGCAATCCAG	CGACCATCAA	CGCAGCCACA	3000
GAGTTGGACA	CGCCCAAGGA	CCTTCAGGTT	TCTGAAACTG	CAGAGACCAG	CCTGACCCTG	3060
CTCTGGAAGA	CACCGTTGGC	CAAAATTTGAC	CGTACCGCC	TCAATTACAG	TCTCCCCACA	3120
GGCCAGTGGG	TGGGAGTGCA	GCTTCCAAGA	AACACCACTT	CCTATGTCTT	GAGAGGCCTG	3180
GAACCAGGAC	AGGAGTACAA	TGTCTCTCTG	ACAGCCGAGA	AAGGCAGACA	CAAGAGCAAG	3240
CCCGCACGTG	TGAAGGCATC	CACTGAACAA	GCCCCGTGAGC	TGGAACACCT	CACCGTGACT	3300
GAGGTTGGCT	GGGATGGCCT	CAGACTCAAC	TGGACCGCGG	CTGACCAGGC	CTATGAGCAC	3360
TTTATCATTC	AGGTGCAGGA	GGCCAACAAG	GTGGAGGCAG	CTCGGAACCT	CACCGTGCCT	3420
GGCAGCCTTC	GGGCTGTGGA	CATACCGGGC	CTCAAGGCTG	CTACGCCTTA	TACAGTCTCC	3480
ATCTATGGGG	TGATCCAGGG	CTATAGAACA	CCAGTGCTCT	CTGCTGAGGC	CTCCACAGGG	3540
GAAACTCCCA	ATTTGGGAGA	GGTCGTGGTG	GCCGAGGTGG	GCTGGGATGC	CCTCAAACCTC	3600
AACTGGACTG	CTCCAGAAGG	GGCCTATGAG	TACTTTTTCA	TTCAGGTGCA	GGAGGCTGAC	3660
ACAGTAGAGG	CAGCCCAGAA	CCTCACCGTC	CCAGGAGGAC	TGAGGTCCAC	AGACCTGCCT	3720
GGGCTCAAAG	CAGCCACTCA	TTATACCATC	ACCATCCGCG	GGGTCACTCA	GGACTTCAGC	3780
ACAACCCCTC	TCTCTGTTGA	AGTCTTGACA	GAGGAGGTTT	CAGATATGGG	AAACCTCACA	3840
GTGACCGAGG	TTAGCTGGGA	TGCTCTCAGA	CTGAAGTGGG	CCACGCCAGA	TGGAACCTAT	3900
GACCAGTTTA	CTATTCAGGT	CCAGGAGGCT	GACCAGGTGG	AAGAGGCTCA	CAATCTCACG	3960
GTTCTTGCCA	GCCTGCGTTC	CATGGAATC	CCAGGCCTCA	GGGCTGGCAC	TCCTTACACA	4020
GTCACCCTGC	ACGGCGAGGT	CAGGGGCCAC	AGCACTCGAC	CCCTTGCTGT	AGAGGTCGTC	4080
CAGTGGGACG	TGCCGCTCCA	GTCCCCGGTG	TCGTAGAGTG	GGGAACGACA	TCTCCAGCAG	4140
ACAGAGGATC	TCCCACAGCT	GGGAGATTTA	GCCGTGTCTG	AGGTTGGCTG	GGATGGCCTC	4200
AGACTCAACT	GGACCGCAGC	TGACAATGCC	TATGAGCACT	TTGTCAATTCA	GGTGCAGGAG	4260
GTCAACAAAG	TGGAGGCAGC	CCAGAACCCTC	ACGTTGCCTG	GCAGCCTCAG	GGCTGTGGAC	4320
ATCCCGGGCC	TCGAGGCTGC	CACGCCTTAT	AGAGTCTCCA	TCTATGGGGT	GATCCGGGGC	4380
TATAGAACAC	CAGTACTCTC	TGCTGAGGCC	TCCACAGCCA	AAGAACCTGA	AATTGGAAAC	4440
TTAAATGTTT	CTGACATAAC	TCCCGAGAGC	TTCAATCTCT	CCTGGATGGC	TACCGATGGG	4500
ATCTTCGAGA	CCTTTACCAT	TGAAATTATT	GATTCCAATA	GTTTGCTGGA	GACTGTGGAA	4560

REPLACEMENT SHEET (RULE 26)

TATAATATCT	CTGGTGCTGA	ACGAACTGCC	CATATCTCAG	GGCTACCCCC	TAGTACTGAT	4620
TTTATTGTCT	ACCTCTCTGG	ACTTGCTCCC	AGCATCCGGA	CCAAAACCAT	CAGTGCCACA	4680
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GTGGATTCTG	GGAAGCTGCT	GGACCCCCAG	GAATTCACAC	TTTCAGGAAC	CCAGAGGAAG	4860
CTGGAGCTTA	GAGGCCTCAT	AACTGGCATT	GGCTATGAGG	TTATGGTCTC	TGGCTTCACC	4920
CAAGGGCATC	AAACCAAGCC	CTTGAGGGCT	GAGATTGTTA	CAGAAGCCGA	ACCGGAAGTT	4980
GACAACTTTC	TGGTTTCAGA	TGCCACCCCA	GACGGTTTCC	GTCTGTCTCTG	GACAGCTGAT	5040
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ACTGAATACG	AAATTGAACT	CTATGGAATA	AGCAAAGGAA	GGCGATCCCA	GACAGTCAGT	5220
GCTATAGCAA	CAACAGCCAT	GGGCTCCCCA	AAGGAAGTCA	TTTCTCAGA	CATCACTGAA	5280
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ACCAGGCTGG	TGAAACTCAT	ACCTGGCGTG	GAGTACCTTG	TCAGCATCAT	CGCCATGAAG	5460
GGCTTTGAGG	AAAGTGAACC	TGTCTCAGGG	TCATTACCA	CAGCTCTGGA	TGGCCCATCT	5520
GGCCTGGTGA	CAGCCAACAT	CACTGACTCA	GAAGCCTTGG	CCAGGTGGCA	GCCAGCCATT	5580
GCCACTGTGG	ACAGTTATGT	CATCTCCTAC	ACAGGCGAGA	AAGTGCCAGA	AATTACACGC	5640
ACGGTGTCCG	GGAACACAGT	GGAGTATGCT	CTGACCGACC	TCGAGCCTGC	CACGGAATAC	5700
ACACTGAGAA	TCTTTGCAGA	GAAAGGGCCC	CAGAAGAGCT	CAACCATCAC	TGCCAAGTTC	5760
ACAACAGACC	TCGATTCTCC	AAGAGACTTG	ACTGCTACTG	AGGTTCACTC	GGAAACTGCC	5820
CTCCTTACCT	GGCGACCCCC	CCGGGCATCA	GTACCCGTT	ACCTGCTGGT	CTATGAATCA	5880
GTGGATGGCA	CAGTCAAGGA	AGTCATTGTG	GGTCCAGATA	CCACCTCCTA	CAGCCTGGCA	5940
GACCTGAGCC	CATCCACCCA	CTACACAGCC	AAGATCCAGG	CACTCAATGG	GCCCCTGAGG	6000
AGCAATATGA	TCCAGACCAT	CTTCAACCACA	ATTGGACTCC	TGTACCCCTT	CCCCAAGGAC	6060
TGCTCCCAAG	CAATGCTGAA	TGGAGACACG	ACCTCTGGCC	TCTACACCAT	TTATCTGAAT	6120
GGTGATAAGG	CTCAGGCGCT	GGAAGTCTTC	TGTGACATGA	CCTCTGATGG	GGGTGGATGG	6180
ATTGTGTTCC	TGAGACGCAA	AAACGGACGC	GAGAAGTCT	ACCAAACTG	GAAGGCATAT	6240
GCTGCTGGAT	TTGGGGACCG	CAGAGAAGAA	TTCTGGCTTG	GGCTGGACAA	CCTGAACAAA	6300
ATCACAGCCC	AGGGGCAGTA	CGAGCTCCGG	GTGGACCTGC	GGGACCATGG	GGAGACAGCC	6360
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GAGGGGTACA	TGGGGACAGC	AGGTGACTCC	ATGGCCTACC	ACAATGGCAG	ATCCTTCTCC	6480
ACCTTTGACA	AGGACACAGA	TTCAGCCATC	ACCAACTGTG	CTCTGTCTAC	AAGGGGCTTC	6540
TGGTACAGGA	ACTGTCACCG	TGTCAACCTG	ATGGGGAGAT	ATGGGGACAA	TAACCACAGT	6600
CAGGGCGTTA	ACTGGTTCCA	CTGGAAGGGC	CACGAACACT	CAATCCAGTT	TGCTGAGATG	6660
AAGCTGAGAC	CAAGCAACTT	CAGAAATCTT	GAAGGCAGGC	GCAAACGGGC	ATAAATTGGA	6720
GGGACCACTG	GGTGAGAGAG	GAATAAGGCG	GCCCAGAGCG	AGGAAAGGAT	TTTACCAAAG	6780
CATCAATACA	ACCAGCCCCA	CCATCGGTCC	ACACCTGGGC	ATTTGGTGAG	AATCAAAGCT	6840
GACCATGGAT	CCCTGGGGCC	AACGGCAACA	GCATGGGCCT	CACCTCCTCT	GTGATTTCTT	6900
TCTTTGCACC	AAAGACATCA	GTCTCCAACA	TGTTTCTGTT	TTGTTGTTTG	ATTCAGCAAA	6960
AATCTCCCAG	TGACAACATC	GCAATAGTTT	TTTACTTCTC	TTAGGTGGCT	CTGGGATGGG	7020
AGAGGGGTAG	GATGTACAGG	GGTAGTTTGT	TTTAGAACCA	GCCGTATTTT	ACATGAAGCT	7080
GTATAATTAA	TTGTCATTAT	TTTTGTTAGC	AAAGATTAAA	TGTGTCATTG	GAAGCCATCC	7140
CTTTTTTTTAC	ATTTCATACA	ACAGAAACCA	GAAAAGCAAT	ACTGTTTCCA	TTTTAAGGAT	7200
ATGATTAATA	TTATTAATAT	AATAATGATG	ATGATGATGA	TGAAACTAA	GGATTTTTCA	7260
AGAGATCTTT	CTTTCCAAAA	CATTTCTGGA	CAGTACCTGA	TTGTATTTTT	TTTTTAAATA	7320
AAAGCACAAAG	TACTTTTGAA	AAAAAA				7346

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

REPLACEMENT SHEET (RULE 26)

(A) NAME/KEY: exon
(B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

GGTTTGGGTG GAGGTGG

17

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

GGAGGTGGTA CCCCCG

17

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

GGTGGTACCC CCGG

14

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..14

REPLACEMENT SHEET (RULE 26)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

GGAGGTGGTA CCCC

14

(2) INFORMATION FOR SEQ ID NO: 6:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 17 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 - (A) NAME/KEY: exon
 - (B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

AGAAAGAACG AAAGGAA

17

(2) INFORMATION FOR SEQ ID NO: 7:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 12 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 - (A) NAME/KEY: exon
 - (B) LOCATION:1..12

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

GGAGGTGGTA CC

12

(2) INFORMATION FOR SEQ ID NO: 8:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 - (A) NAME/KEY: exon
 - (B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

GGAGCGATGG CTTCCA

16

REPLACEMENT SHEET (RULE 26)

004220" x 3445550

(2) INFORMATION FOR SEQ ID NO: 9:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

AAAGGAACGG GAGCG

15

(2) INFORMATION FOR SEQ ID NO: 10:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

GGTCGGTTTG GGTGG

15

(2) INFORMATION FOR SEQ ID NO: 11

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

CTTACAGGTC CGTTGA

16

(2) INFORMATION FOR SEQ ID NO: 12:

REPLACEMENT SHEET (RULE 26)

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 15 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

GGCCGTGTTC GCTGT

15

(2) INFORMATION FOR SEQ ID NO: 13:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 16 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

TCACCCCTCT TTCTGG

16

(2) INFORMATION FOR SEQ ID NO: 14:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 14 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

GGACACCGAC ACGG

14

(2) INFORMATION FOR SEQ ID NO: 15:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 14 base pairs

REPLACEMENT SHEET (RULE 26)

- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

AACGGGAGCG ATGG

14

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

ATCTCGGGGT CGTC

14

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

AAAGAACGAA AGGAA

15

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 11 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

REPLACEMENT SHEET (RULE 26)

- (ii) MOLECULE TYPE: DNA (genomic)
- (ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..11
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

GGTGGTACCC C

11

(2) INFORMATION FOR SEQ ID NO: 19:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 11 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..11
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

CCCGGTACTG A

11

(2) INFORMATION FOR SEQ ID NO: 20:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 13 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..13
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

CCACAGAAAG AAC

13

(2) INFORMATION FOR SEQ ID NO: 21:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 17 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

GGTTTGGGTG GAGGTGG

17

(2) INFORMATION FOR SEQ ID NO: 22:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 17 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

GGAGGTGGTA CCCCCGG

17

(2) INFORMATION FOR SEQ ID NO: 23:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 14 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

GGTGGTACCC CCGG

14

(2) INFORMATION FOR SEQ ID NO: 24:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 14 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..14

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004220/2324550

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

GGAGGTGGTA CCCC

14

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 17 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

AGAAAGAACG AAAGGAA

17

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 12 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..12

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

GGAGGTGGTA CC

12

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 16 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

REPLACEMENT SHEET (RULE 26)

004220" 4343560

GGAGCGATGG CTTCCA

16

(2) INFORMATION FOR SEQ ID NO: 28:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

AAAGGAACGG GAGCG

15

(2) INFORMATION FOR SEQ ID NO: 29:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

GGTCGGTTTG GGTGG

15

(2) INFORMATION FOR SEQ ID NO: 30:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

CTTACAGGTC CGTTGA

16

(2) INFORMATION FOR SEQ ID NO: 31:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

GGCCGTGTTC GCTGT

15

(2) INFORMATION FOR SEQ ID NO: 32:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

TCACCCCTCT TTCTGG

16

(2) INFORMATION FOR SEQ ID NO: 33:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

GGACACCGAC ACGG

14

(2) INFORMATION FOR SEQ ID NO: 34:

- (i) SEQUENCE CHARACTERISTICS:

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004220.294555

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

AACGGGAGCG ATGG

14

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

ATCTCGGGGT CGTC

14

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

AAAGAACGAA AGGAA

15

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 11 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

REPLACEMENT SHEET (RULE 26)

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: exon

(B) LOCATION:1..11

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

GGTGGTACCC C

11

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: exon

(B) LOCATION:1..11

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

CCCGGTACTG A

11

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: exon

(B) LOCATION:1..13

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

CCACAGAAAG AAC

13

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

REPLACEMENT SHEET (RULE 26)

004270 324560

(ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

GGTTTGGGTG GAGGTGG

17

(2) INFORMATION FOR SEQ ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 17 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

GGAGGTGGTA CCCCCGG

17

(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 14 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

GGTGGTACCC CCGG

14

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 14 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
 (A) NAME/KEY: exon

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(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

GGAGGTGGTA CCCC

14

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

AGAAAGAACG AAAGGAA

17

(2) INFORMATION FOR SEQ ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..12

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

GGAGGTGGTA CC

12

(2) INFORMATION FOR SEQ ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: exon
- (B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

REPLACEMENT SHEET (RULE 26)

GGAGCGATGG CTTCCA

16

(2) INFORMATION FOR SEQ ID NO: 47:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 - (A) NAME/KEY: exon
 - (B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

AAAGGAACGG GAGCG

15

(2) INFORMATION FOR SEQ ID NO: 48:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 - (A) NAME/KEY: exon
 - (B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

GGTCGGTTTG GGTGG

15

(2) INFORMATION FOR SEQ ID NO: 49:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 - (A) NAME/KEY: exon
 - (B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

CTTACAGGTC CGTTGA

16

(2) INFORMATION FOR SEQ ID NO: 50:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 - (A) NAME/KEY: exon
 - (B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

GGCCGTGTTT GCTGT

15

(2) INFORMATION FOR SEQ ID NO: 51:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 - (A) NAME/KEY: exon
 - (B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

TCACCCCTCT TTCTGG

16

(2) INFORMATION FOR SEQ ID NO: 52:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 - (A) NAME/KEY: exon
 - (B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

GGACACCGAC ACGG

14

(2) INFORMATION FOR SEQ ID NO: 53:

REPLACEMENT SHEET (RULE 26)

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 14 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

AACGGGAGCG ATGG

14

(2) INFORMATION FOR SEQ ID NO: 54:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 14 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

ATCTCGGGGT CGTC

14

(2) INFORMATION FOR SEQ ID NO: 55:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 15 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- (ix) FEATURE:
 (A) NAME/KEY: exon
 (B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

AAAGAACGAA AGGAA

15

(2) INFORMATION FOR SEQ ID NO: 56:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 11 base pairs
 (B) TYPE: nucleic acid

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(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: exon
(B) LOCATION:1..11

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

GGTGGTACCC C

11

(2) INFORMATION FOR SEQ ID NO: 57:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: exon
(B) LOCATION:1..11

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

CCCGGTACTG A

11

(2) INFORMATION FOR SEQ ID NO: 58:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: exon
(B) LOCATION:1..13

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

CCACAGAAAG AAC

13